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RESPIRATORY CARE

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For Patients With Asthma

Twice-Daily

Serevent®

(salmeterol xinafoate)

Inhalation Aerosol

Morning and Evening Inhalation for Active Days and Restful Nights

SEREVENT is indicated for maintenance treatment of asthma and prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting β_2-agonists.

Dosing should be two puffs (42 µg) of SEREVENT Inhalation Aerosol, twice daily, morning and evening, approximately 12 hours apart.

***IMPORTANT:** SEREVENT should not be used to relieve acute asthma symptoms.*

The most common drug-related adverse events reported in clinical trials were headache (10%), tremor (3%), and cough (3%).[1]

Please consult Brief Summary of Prescribing Information on adjacent pages.

Serevent®
(salmeterol xinafoate)
Inhalation Aerosol

BRIEF SUMMARY

Bronchodilator Aerosol
For Oral Inhalation Only

The following is a brief summary only. Before prescribing, see complete prescribing information in Serevent® Inhalation Aerosol product labeling.

CONTRAINDICATIONS: Serevent® Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to any of the components.

WARNINGS: 1. Not for Use to Treat Acute Symptoms; Watch for Increased Need for Short-Acting Beta$_2$-Agonists: Serevent® Inhalation Aerosol should not be used to relieve acute asthma symptoms. If the patient's short-acting, inhaled beta$_2$-agonist becomes less effective, e.g., the patient needs more inhalations than usual, medical evaluation must be obtained immediately and increasing use of Serevent Inhalation Aerosol in this situation is inappropriate. Serevent Inhalation Aerosol should not be used more frequently than twice daily (morning and evening) at the recommended dose. When prescribing Serevent Inhalation Aerosol, patients must be provided with a short-acting, inhaled beta$_2$-agonist (e.g., albuterol) for treatment of symptoms that occur despite regular twice-daily (morning and evening) use of Serevent.

Asthma may deteriorate acutely over a period of hours or chronically over several days. In this setting, increased use of inhaled, short-acting beta$_2$-agonists is a marker of destabilization of asthma and requires re-evaluation of the patient and consideration of alternative treatment regimens, especially inhaled or systemic corticosteroids. If the patient uses four or more inhalations per day of a short-acting beta$_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

2. Use With Short-Acting Beta$_2$-Agonists: When patients begin treatment with Serevent Inhalation Aerosol, those who have been taking short-acting, inhaled beta$_2$-agonists on a regular daily basis should be advised to discontinue their regular daily-dosing regimen and should be clearly instructed to use short-acting, inhaled beta$_2$-agonists only for symptomatic relief if they develop asthma symptoms while taking Serevent Inhalation Aerosol (see PRECAUTIONS: Drug Interactions).

3. Serevent Inhalation Aerosol Is Not a Substitute for Oral or Inhaled Corticosteroids: Patients must be warned not to stop or reduce corticosteroid therapy without medical advice, even if they feel better when they are being treated with Serevent.

4. Do Not Exceed Recommended Dose: As with other beta-adrenergic aerosols, Serevent Inhalation Aerosol should not be used in excess. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT_C interval, which has the potential for producing ventricular arrhythmias.

5. Paradoxical Bronchospasm: As with other inhaled asthma medications, paradoxical bronchospasm (which can be life-threatening) has been reported following the use of Serevent Inhalation Aerosol. If it occurs, treatment with Serevent Inhalation Aerosol should be discontinued immediately and alternative therapy instituted.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of Serevent Inhalation Aerosol, as demonstrated by rare cases of urticaria, angioedema, rash, and bronchospasm.

PRECAUTIONS:

General: 1. Use with Spacer or Other Devices: The safety and effectiveness of Serevent® Inhalation Aerosol when used with a spacer or other devices have not been adequately studied.

2. Cardiovascular and Other Effects: No effect on the cardiovascular system is usually seen after the administration of inhaled salmeterol in recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of Serevent Inhalation Aerosol and may require discontinuation of the drug. Salmeterol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically significant changes in systolic and/or diastolic blood pressure, pulse rate, and electrocardiograms have been seen infrequently in individual patients in controlled clinical studies with salmeterol.

3. Metabolic Effects: Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. No effects on glucose have been seen with Serevent Inhalation Aerosol at recommended doses. Administration of beta$_2$-adrenoceptor agonists may cause a decrease in serum potassium, possibly through intracellular shunting, which has the potential to increase the likelihood of arrhythmias. The decrease is usually transient, not requiring supplementation.

Clinically significant changes in blood glucose and/or serum potassium were seen rarely during clinical studies with long-term administration of Serevent Inhalation Aerosol at recommended doses.

Information for Patients: See illustrated Patient's Instructions for Use. **SHAKE WELL BEFORE USING.** Patients should be given the following information:

1. Not for Use to Treat Acute Symptoms: Serevent Inhalation Aerosol is not meant to relieve acute asthmatic symptoms. Acute symptoms should be treated with an inhaled, short-acting bronchodilator that has been prescribed by a physician for symptom relief.

2. Do Not Exceed Recommended Dose: The bronchodilator action of salmeterol usually lasts for at least 12 hours. Therefore it should not be used more often than every 12 hours.

3. Use with Other Medications: While using Serevent Inhalation Aerosol, other inhaled medicines should be taken only as directed by the physician.

4. Use with Short-Acting, Inhaled Beta-Agonists: While using Serevent Inhalation Aerosol, medical attention should be sought immediately if the short-acting bronchodilator treatment becomes less effective for symptom relief, if more inhalations than usual are needed, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed. If the patient uses four or more inhalations per day of a short-acting beta$_2$-agonist on a regular basis, or if more than one canister (200 inhalations per canister) is used in an 8-week period, then the patient should see the physician for re-evaluation of treatment.

Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain, related to the use of additional beta$_2$-agonist.

5. Use of Systemic or Inhaled Steroids: Serevent Inhalation Aerosol does not replace oral or inhaled corticosteroids; the dosage of these medicines should not be changed and they should not be stopped without consulting the physician, even if the patient feels better.

6. Use for Exercise-Induced Bronchospasm: When using Serevent Inhalation Aerosol to prevent exercise-induced bronchospasm, the dose should be administered at least 30 to 60 minutes before exercise.

Drug Interactions: ***Short-Acting Beta-Agonists:*** In the two 3-month, repetitive-dose clinical trials (n=184), the mean daily need for additional beta$_2$-agonist use was 1 to 1½ inhalations per day, but some patients used more. Eight percent of patients used at least eight inhalations per day at least on one occasion. Six percent used 9 to 12 inhalations at least once. There were 15 patients (8%) who averaged over four inhalations per day. Four of these used an average of 8 to 11 inhalations per day. In these 15 patients there was no observed increase in frequency of cardiovascular adverse events. The safety of concomitant use of more than eight inhalations per day of short-acting beta$_2$-agonists with Serevent® (salmeterol xinafoate) Inhalation Aerosol has not been established. In 15 patients who experienced worsening of asthma while receiving Serevent Inhalation Aerosol, nebulized albuterol (one dose in most) led to improvement in FEV_1 and no increase in occurrence of cardiovascular adverse events.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: Salmeterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants because the action of salmeterol on the vascular system may be potentiated by these agents.

Corticosteroids and Cromoglycate: In clinical trials, inhaled corticosteroids and/or inhaled cromolyn sodium did not alter the safety profile of Serevent Inhalation Aerosol when administered concurrently.

Methylxanthines: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving Serevent Inhalation Aerosol has not been completely evaluated. In one clinical trial, 87 patients receiving Serevent Inhalation Aerosol 42 mcg twice daily concurrently with a theophylline product had adverse event rates similar to those in 71 patients receiving Serevent Inhalation Aerosol without theophylline. Resting heart rates were slightly higher in the patients on theophylline but were little affected by Serevent Inhalation Aerosol therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In an 18-month oral carcinogenicity study in CD-mice, salmeterol xinafoate caused a dose-related increase in the incidence of smooth muscle hyperplasia, cystic glandular hyperplasia, and leiomyomas of the uterus and a dose-related increase in the incidence of cysts in the ovaries. A higher incidence of leiomyosarcomas was not statistically significant; tumor findings were observed at oral doses of 1.4 and 10 mg/kg, which gave 9 and 63 times, respectively, the human exposure based on rodent:human AUC comparisons.

Salmeterol caused a dose-related increase in the incidence of mesovarian leiomyomas and ovarian cysts in Sprague Dawley rats in a 24-month inhalation/oral carcinogenicity study. Tumors were observed in rats receiving doses of 0.68 and 2.58 mg/kg per day (about 55 and 215 times the recommended clinical dose [mg/m^2]). These findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

No significant effects occurred in mice at 0.2 mg/kg (1.3 times the recommended clinical dose based on comparisons of the AUCs) and in rats at 0.21 mg/kg (15 times the recommended clinical dose on a mg/m^2 basis).

Salmeterol xinafoate produced no detectable or reproducible increases in microbial and mammalian gene mutation *in vitro*. No blastogenic activity occurred *in vitro* in human lymphocytes or *in vivo* in a rat micronucleus test. No effects on fertility were identified in male and female rats treated orally with salmeterol xinafoate at doses up to 2 mg/kg orally (about 160 times the recommended clinical dose on a mg/m^2 basis).

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** No significant effects of maternal exposure to oral salmeterol xinafoate occurred in the rat at doses up to the equivalent of about 160 times the recommended clinical dose on a mg/m^2 basis. Dutch rabbit fetuses exposed to salmeterol xinafoate *in utero* exhibited effects characteristically resulting from beta-adrenoceptor stimulation; these included precocious eyelid openings, cleft palate, sternebral fusion, limb and paw flexures, and delayed ossification of the frontal cranial bones. No significant effects occurred at 0.6 mg/kg given orally (12 times the recommended clinical dose based on comparison of the AUCs).

New Zealand White rabbits were less sensitive since only delayed ossification of the frontal bones was seen at 10 mg/kg given orally (approximately 1,600 times the recommended clinical dose on a mg/m^2 basis). Extensive use of other beta-agonists has provided no evidence that these class effects in animals are relevant to use in humans. There are no adequate and well-controlled studies with Serevent Inhalation Aerosol in pregnant women. Serevent Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery: There are no well-controlled human studies that have investigated effects of salmeterol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of Serevent Inhalation Aerosol during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers: Plasma levels of salmeterol after inhaled therapeutic doses are very low (85 to 200 pg/mL) in humans. In lactating rats dosed with radiolabeled salmeterol, levels of radioactivity were similar in plasma and milk. In rats, concentrations of salmeterol in plasma and milk were similar. The xinafoate moiety is also transferred to milk in rats at concentrations of about half the corresponding level in plasma. However, since there is no experience with use of Serevent Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when salmeterol xinafoate is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Serevent Inhalation Aerosol in children younger than 12 years of age have not been established.

Geriatric Use: Of the total number of patients who received Serevent Inhalation Aerosol in all clinical studies, 241 were 65 years and older. Geriatric patients (65 years and older) with reversible obstructive airway disease were evaluated in four well-controlled studies of 3 weeks' to 3 months' duration. Two placebo-controlled, crossover studies evaluated twice-daily dosing with salmeterol for 21 to 28 days in 45 patients. An additional 75 geriatric patients were treated with salmeterol for 3 months in two large parallel-group, multicenter studies. These 120 patients experienced increases in AM and PM peak expiratory flow rate and decreases in diurnal variation in peak expiratory flow rate similar to responses seen in the total populations of the two latter studies. The adverse event type and frequency in geriatric patients were not different from those of the total populations studied.

No apparent differences in the efficacy and safety of Serevent Inhalation Aerosol were observed when geriatric patients were compared with younger patients in clinical trials. As with other beta$_2$-agonists, however, special caution should be observed when using Serevent Inhalation Aerosol in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug. Based on available data, no adjustment of salmeterol dosage in geriatric patients is warranted.

ADVERSE REACTIONS: Adverse reactions to salmeterol are similar in nature to reactions to other selective beta$_2$-adrenoceptor agonists, i.e., tachycardia; palpitations; immediate hypersensitivity reactions, including urticaria, angioedema, rash, bronchospasm (see WARNINGS); headache; tremor; nervousness; and paradoxical bronchospasm (see WARNINGS).

Two multicenter, 12-week, controlled studies have evaluated twice-daily doses of Serevent® Inhalation Aerosol in patients 12 years of age and older with asthma. The following table reports the incidence of adverse events in these two studies.

Serevent® (salmeterol xinafoate) Inhalation Aerosol

Adverse Experience Incidence in Two Large 12-Week Clinical Trials*

Adverse Event Type	Percent of Patients		
	Placebo n=187	Serevent 42 mcg b.i.d. n=184	Albuterol 180 mcg q.i.d. n=185
Ear, nose, and throat			
Upper respiratory tract infection	13	14	16*
Nasopharyngitis	12	14	11
Disease of nasal cavity/sinus	4	6	1
Sinus headache	2	4	<1
Gastrointestinal			
Stomachache	0	4	0
Neurological			
Headache	23	28	27
Tremor	2	4	3
Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

* The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or nondrug related by the investigator) that occurred at a rate of over 3% in the Serevent® (salmeterol xinafoate) Inhalation Aerosol treatment group and were more common in the Serevent Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the Serevent Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.
Ear, Nose, and Throat: Rhinitis, laryngitis.
Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.
Hypersensitivity: Urticaria.
Mouth and Teeth: Dental pain.
Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.
Neurological: Nervousness, malaise/fatigue.
Respiratory: Tracheitis/bronchitis.
Skin: Rash/skin eruption.
Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

OVERDOSAGE: Overdosage with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdosage with salmeterol can lead to clinically significant prolongation of the QT_C interval, which can produce ventricular arrhythmias. Other signs of overdosage may include hypokalemia and hyperglycemia.

In these cases, therapy with Serevent® Inhalation Aerosol and all beta-adrenergic–stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of Serevent Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively.

Dialysis is not appropriate treatment for overdosage of Serevent Inhalation Aerosol.

Allen & Hanburys
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

September 1994
RL-137

Reference: *1. Data on file, Glaxo Inc.*

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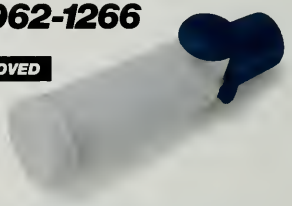

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REFERENCES 1. Data on file. HealthScan Products Inc. 2. Wheeler BB, Bollers ND: Initial experience with a novel spacer device. (Presented at the 1993 meeting of the American Academy of Allergy and Immunology) * U.S. Patent No. 5,040,527 OA760004-0 © 1994. HealthScan Products Inc

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Editorials and Commentaries To Note

Drug Delivery by Nebulization: "Reality Testing" (editorial)—G Smaldone. J Aerosol Med 1994;7(3):213-216. (Pertains to Phipps & Gonda paper abstracted on Page 1136, Hurley et al on Page 1136, Nerbrink et al on Page 1138, and Knoch et al on Page 1141.)

The Fallacy of the Ecological Fallacy: The Potential Misuse of a Concept and the Consequences—S Schwartz. Am J Public Health 1994;84:819-824.

Assessment of Reversibility of Airflow Obstruction—JA Van Noord, J Smeets, J Clément, KP Van De Woestijne, M Demedts. Am J Respir Crit Care Med 1994;150:551.

The application of the forced oscillation technique to assess reversibility of airflow obstruction was compared with that of indices of forced expiration and plethysmographic airway resistance (Raw). In 125 patients with airflow obstruction, we measured total respiratory resistance (Rrs) and reactance (Xrs), Raw and specific airway conductance (sGaw), maximal flow-volume curves and forced expiratory volume in 1 s (FEV_1), before and 30 min after 2 × 20 μg salbutamol by MDI. Salbutamol induced significant change in mean value of all measured indices. The changes in impedance data consisted of decrease in mean value and of negative frequency dependence of Rrs, an increase in Xrs with slight decrease of its positive frequency dependence. Multivariate analysis of differences between pre- and postbronchodilator values showed that the single indices with the greatest sensitivity to detect the effect of salbutamol were, in decreasing order, (1) in relative change (% baseline value): Raw, Rrs at 6 Hz (Rrs_6), forced vital capacity (FVC), FEV_1, and (2) in absolute change: FVC, sGaw or Raw, Rrs_6, FEV_1, maximal expiratory flow (MEF_{50}). The effect of salbutamol was described best in (1) by a combination of Raw and FVC and in (2) by sGaw and FVC. For individual detection of bronchodilator effect, threshold values were calculated from mean reproducibility of the three baseline values of the various indices, attempting to estimate whether response to a bronchodilator is statistically significant. The greatest number of significant responses were observed for Raw, sGaw, FEV_1, and FVC in that succession, Rrs_6 being markedly less sensitive. This discrepancy is due to the lack of Rrs_6 response to bronchodilators in patients with severe airway obstruction. We conclude that, although Rrs_6 is applicable as a test in clinical practice for bronchodilation, it is less sensitive than Raw in patients with clearly abnormal baseline lung function.

Counseling Adolescents for Smoking Prevention: A Survey of Primary Care Physicians and Dentists—DI Gregorio. Am J Public Health 1994;84:1151.

Pediatricians, family practitioners, and dentists were questioned in the spring of 1992 about whether they counseled adolescent patients (10 through 18 years old) not to smoke. Of the 674 questionnaires distributed, 443 (66%) were returned and analyzed. Most practitioners could not estimate cigarette use among their adolescent patients. Prevention counseling occurred infrequently, and least often among younger patients. Physicians were more likely than dentists to counsel adolescents. The data highlight the need for continuing training of primary health care practitioners about the importance of counseling adolescents not to smoke.

Effect of Endogenous and Inhaled Nitric Oxide on the Ventilation-Perfusion Relationships in Oleic-Acid Lung Injury—C Putensen, J Räsänen, JB Downs, FA Lopez. Am J Respir Crit Care Med 1994;150:330.

Previous investigations have shown that the ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatch caused by acute lung injury can be alleviated either by inducing vasodilation in ventilated lung units with inhaled nitric oxide (NO) or by inhibiting the synthesis of endogenous NO, which opposes hypoxic pulmonary vasoconstriction. To determine the effects of a combination of these interventions, we evaluated cardiopulmonary function and $\dot{V}_A/\dot{Q}$ distributions in 10 dogs with oleic acid-induced lung injury. Each animal received, in random order, zero or 40 ppm of NO in inspiratory gas, with and without intravenous infusion of N^G-monomethyl-L-arginine (L-NMMA) (5 mg/kg/h). The multiple inert-gas elimination technique was used to estimate $\dot{V}_A/\dot{Q}$ distributions. Systemic L-NMMA administration alone did not affect $\dot{V}_A/\dot{Q}$ inequality and gas exchange, but increased pulmonary and systemic vascular resistance. Inhaled NO improved gas exchange by redistributing blood flow from shunt units to lung units with a nearly ideal $\dot{V}_A/\dot{Q}$ ratio, without affecting pulmonary or systemic vascular resistance. Improved $\dot{V}_A/\dot{Q}$ matching and gas exchange was most pronounced when NO was inhaled in the presence of systemic L-NMMA. Inhalation of NO reversed the pulmonary but not the systemic vasoconstriction caused by L-NMMA. These results suggest that endogenous NO release is not limited to hypoxic lung regions in animals with oleic acid-induced lung injury. Inhaled NO reversed L-NMMA-induced pulmonary vasoconstriction and improved $\dot{V}_A/\dot{Q}$ matching by selectively dilating the pulmonary vasculature in ventilated lung units.

Effects of a Restricted Work-Site Smoking Policy on Employees Who Smoke—J Brigham, J Gross, ML Stitzer, LJ Felch. Am J Public Health 1994;84:773.

OBJECTIVES: This study evaluated the biological and subjective consequences observed in individual smokers after implementation of a workplace smoking-restriction policy. METHODS: Employees were evaluated for 4 weeks before and 4 weeks after their workplace became smokefree (n = 34). A comparison group of smokers whose work-site smoking was unrestricted served as controls (n = 33). Daily exposure to tobacco constituents and withdrawal effects were measured. RESULTS: Smokers at the restricted site had verified smoking reduction (mean = four cigarettes per day) and significantly reduced nicotine and carbon monoxide during the work shift. There were increases in ratings of some common withdrawal symptoms (cravings/urges, concentration difficulties, increased eating, depression). No evidence of compensatory smoking during nonwork hours was found. Overall tobacco exposure, as measured in saliva cotinine, showed a nonsignificant 15% decline. CONCLUSIONS: Workplace smoking restriction markedly altered smoking patterns (ie, reduced daytime smoking) and reduced cotinine levels to an amount consistent with cigarette

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reduction. Thus, work-site smoking restriction may promote meaningful, albeit limited, reductions in tobacco exposure and consequent health risks.

Evaluation of Definitions for Adult Respiratory Distress Syndrome—WA Knaus, X Sun, RB Hakim, DP Wagner. Am J Respir Crit Care Med 1994;150:311.

We conducted a cohort study of 423 intensive care unit (ICU) admissions with a primary clinical diagnosis of acute respiratory failure, a P_{aO_2}/F_{IO_2} on ICU admission of < 300 mm Hg, and an ICD-9 discharge diagnosis of adult respiratory distress syndrome (ARDS) (518.5 or 518.82) drawn from a nationally representative database of 17,440 ICU admissions to evaluate current and proposed revisions for definitions of ARDS. A variety of nonpulmonary physiologic risk factors, from shock to elevated serum bilirubin measurements, were significant ($p < 0.01$) for hospital mortality. Multivariable analysis using the admission APACHE III score, primary ICU admission diagnosis, and treatment location before ICU admission provided greater accuracy in prediction (ROC = 0.80) than the individual P_{aO_2}/F_{IO_2} (ROC = 0.68). Patients were given an individual risk of hospital mortality based on their admission APACHE III score, treatment location before ICU admission, and ICU admitting diagnosis. Dividing the patient population into groups using a $P_{aO_2}/F_{IO_2} \leq 150$ resulted in a wide range of individual risk for hospital mortality, from < 10 to > 90% in both groups. We conclude that ARDS is a complex clinical entity with a variety of pulmonary and nonpulmonary risk factors for both its development and its prognosis. Current and proposed categorical definitions based on the severity of hypoxemia result in a wide distribution of individual patient risks. Use of these findings in the design and conduct of future clinical trials would improve the evaluation of new therapies.

Evaporation of Aqueous Aerosols Produced by Jet Nebulizers: Effects on Particle Size and Concentration of Solution in the Droplets—PR Phipps, I Gonda. J Aerosol Med 1994;7:239.

Aqueous droplets produced by jet nebulizers can lose water by evaporation prior to entry into the patient's mouth, or a sizing device. Evaporation causes increase in the concentration of the solution in the droplet and reduction in size. These changes can complicate interpretation of results from experiments such as in vitro particle sizing or human respiratory tract deposition. We present experimental data obtained by nebulization of isotonic saline using a variety of aerosol delivery systems employing jet nebulizers. The impact of the evaporation phenomena is particularly great when a large volume of dry dilution air is mixed with the aerosol stream—a situation that is quite common in aerosol experiments. The experimental results approach the values calculated from the theoretical mass balance models in the limit of equilibrium between the droplets and the surrounding atmosphere.

Assessment of Antibiotic Aerosol Generation Using Commercial Jet Nebulizers—PK Hurley, SW Smye, H Cunliffe. J Aerosol Med 1994;7:217.

The performance of 14 commercial jet nebulisers has been assessed: Unineb, Suremist (Unimed (UK) Ltd), Micro-Cirrus (Intersurgical Ltd), Pulmo-Neb (DeVilbiss Health Care UK Ltd), Side-Stream (Medic-Aid Ltd), Micro-Neb III (Lifecare Ltd), RespirGard (Marquest Medical Products Inc), Aeromist, Venticaire (S and W Vickers Ltd), Up-Draft II, Ava-Neb, Up-Draft (Hudson Respiratory Care Inc), Bennett/Twin, Raindrop (Puritan-Bennett Corporation). The units were operated with a high flow compressor (Maxi III, Medix Ltd) at 101/min. Performance was assessed by measuring the fraction of the initial mass of drug released as an aerosol and nebulisation time for initial drug volumes of 2-6 mL, and the mass median diameter and mass fraction of the aerosol in particles < 5.17 μm diameter. The Side-Stream nebuliser gave the best performance, although incorporation of a filter to trap exhaled antibiotic may prove difficult. The Micro-Cirrus generated a particularly fine aerosol. The Raindrop nebuliser performed well, while the Up-Draft II nebulised efficiently but was associated with extended nebulisation times, which may limit its utility.

Low Birthweight at Term and the Timing of Fetal Exposre to Maternal Smoking—Am J Public Health 1994;84:1127.

OBJECTIVES: This study was undertaken to evaluate the risk of small-for-gestational-age birth for women who stop smoking or begin to smoke during pregnancy. METHODS: Women with term singleton pregnancies from a hospital-based cohort of 11 177 were classified as (1) nonsmokers; (2) smoked throughout pregnancy; (3) smoked during first trimester only; (4) smoked during first and second trimesters only; and (5) smoked during second and third trimesters or during third trimester only. Risk of small-for-gestional-age birth according to smoking category was estimated and adjusted for confounding factors by logistic regression. RESULTS: Women who stopped smoking by the third trimester were not at increased risk of small-for-gestional-age birth compared with nonsmokers. Women who began smoking during the second or third trimester had an elevated risk of small-for-gestational-age birth (odds ratio [OR] 1.83; 95% confidence interval [CI] = 1.25, 2.67) similar to that for women who smoked throughout pregnancy (OR = 2.20; 95% CI = 1.90, 2.54). Risk of small-for-gestional-age birth increased with the number of cigarettes smoked during the third trimester. CONCLUSIONS: It is during the third trimester that smoking retards fetal growth, presenting a compelling opportunity for smoking cessation interventions. Programs must emphasize the importance of not resuming smoking late in pregnancy.

Mathematical Coupling Explains Dependence of Oxygen Consumption on Oxygen Delivery in ARDS—PT Phang, KF Cunningham, JJ Ronco, BR Wiggs, JA Russell. Am J Respir Crit Care Med 1994;150:318.

Because of potential for mathematical coupling of measurement errors in shared variables used to calculate oxygen consumption ($Fick\dot{V}_{O_2}$) and oxygen delivery (D_{O_2}), we asked whether determination of the $Fick\dot{V}_{O_2}$-D_{O_2} relationship in individual patients with ARDS was statistically valid. We studied 17 clinically resuscitated patients with severe ARDS, measuring $Fick\dot{V}_{O_2}$, Calorimetric $\dot{V}_{O_2}$ (using analysis of respiratory gases), and D_{O_2} at regular intervals while D_{O_2} was increased using an infusion of dobutamine. Overall, we found that D_{O_2} (pre 482 ± 143, post 616 ± 170 mL O_2/min · m^2, $p < 0.01$) and $Fick\dot{V}_{O_2}$ (pre 130 ± 23, post 147 ± 24 mL · O_2/min · m^2, $p < 0.02$) increased significantly with dobutamine infusion, but $Calorimetric\dot{V}_{O_2}$ measured simultaneously did not change (pre 128 ± 22, post 128 ± 22 mL O_2/min · m^2, p = NS). In addition, unpooled weighted slope for $Fick\dot{V}_{O_2}$ versus D_{O_2} (0.06) was significantly different from zero, but unpooled weighted slope for $Calorimetric\dot{V}_{O_2}$ versus D_{O_2} (0.01) was not significantly different from zero. Slopes of the $Fick\dot{V}_{O_2}$-D_{O_2} relationship were significant for only three individual patients. Using methods by Stratton and colleagues to analyze the effect of mathematical coupling in the $Fick\dot{V}_{O_2}$-D_{O_2} relationship, we found that in all patients the slope of measurement errors was greater than observed slope and that observed slope was greater than estimated true slope. Estimated true slope of the $Fick\dot{V}_{O_2}$-D_{O_2} relationship in all individual patients was not significant. Therefore, we suggest that determination of the $Fick\dot{V}_{O_2}$-D_{O_2} relationship in individual patients who are resuscitated and hemodynamically stable is most often not statistically significant. Furthermore, we suggest that mathematical coupling of random error in the measurement of shared variables could explain finding dependence of $Fick\dot{V}_{O_2}$ on D_{O_2} in clinically resuscitated individual patients with severe ARDS.

Nonbronchodilator Effects of Inhaled β_2 Agonists: Greater Protection against Adenosine Monophosphate- Than Methacholine-Induced Bronchoconstriction in Asthma—BJ O'Connor, RW Fuller, PJ Barnes. Am J Respir Crit Care Med 1994;150:381.

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There has been controversy about possible beneficial effects of β agonists on airway function in asthma, in addition to their effects on airway smooth muscle. We compared the protective effects of terbutaline on bronchoconstrictor responses to methacholine, which constricts smooth muscle directly, adenosine 5'-monophosphate (AMP), which acts indirectly by mast cell activation, and sodium metabisulfite (MBS), which stimulates sensory nerves, in 15 mild asthmatic subjects in a randomized double-blind study carried out in two phases. In the first phase 12 subjects inhaled two doses of 0.5 and 2.5 mg terbutaline or placebo administered as a dry powder (Tubohaler®) 20 min before challenge with methacholine and AMP. Each subject received increasing doubling doses of methacholine and AMP nebulized from a dosimeter. Challenges were terminated when FEV_1 fell by 20% from baseline (PC_{20}). In the second phase 10 subjects (seven of whom had participated in Phase 1) inhaled 0.5 mg terbutaline or placebo before similar challenge with methacholine and MBS. In Phase 1, terbutaline inhibited the bronchoconstrictor response to methacholine by 2.1 and 3.3 doubling doses but caused a significantly greater inhibition of the response to AMP of 3.4 and 4.8 doubling doses after 0.5 and 2.5 mg, respectively. In the second phase, 0.5 mg terbutaline had equivalent effects on responses to both methacholine and MBS of 2.6 and 2.2 doubling dilutions, respectively. This effect on methacholine and MBS implies functional antagonism of airway smooth muscle. The enhanced effect on AMP implies an additional non-smooth muscle action that may involve suppression of airway mast cell function.

Why Do Medical Nebulizers Differ in Their Output and Particle Size Characteristics?—O Nerbrink, M Dahlbäck, HC Hansson. J Aerosol Med 1994;7:259.

Previous work done on the characterization of nebulizers has focused on gravimetrical output and particle/droplet size distribution at various air flow rates. This paper investigates six different nebulizers, with regard to droplet generation and separation properties, at a single air flow rate. Droplet generation and separation properties were measured with laser diffraction and impactor techniques. For each of the nebulizers the air velocity was calculated and both liquid and air volumetric flow rate was measured. The primary generated droplets (nebulizer without impaction baffle) had a mean size of between 15 μm and > 500 μm. The secondary generated droplets (nebulizer with baffle) were in the size range of 1 to 10 μm. It was found that the baffle system of the investigated nebulizers could be described according to ordinary impaction theory. The mass median diameters (MMD) of these nebulizers were found to be dependent on air velocity (v_g) and ratio of liquid to air volumetric flow rate (Q_l/Q_a). In all of the nebulizers, between 93% and 99% of the generated primary droplets were caught by the baffle system, which resulted in a very low output. Thus, the nebulizers examined do not appear to be optimised, with regard to observed droplet generation and baffle arrangements, if secondary droplets with a size ≈ 1 μm are desired. By changing the design at the primary generation point, air velocity (v_g) and liquid to air flow rate (Q_l/Q_a), the primary generated droplet size could be decreased. This would result in an increase in the number concentration of smaller droplets that pass the baffle system. As changes in v_g affect Q_l/Q_a, and both v_g and Q_l/Q_a

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[1] Yang K Tobin M A Prospective Study of Indexes Predicting the Outcome of Trials of Weaning from Mechanical Ventilation. N Engl J Med 1991; 324: 1445-1448

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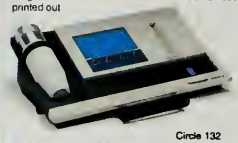

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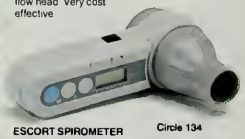

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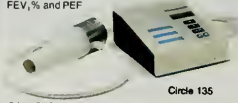

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separately influence the size distribution and thus output, nebulizer performance becomes difficult to control in a desired way. This suggests that it will be difficult to change the droplet size and at the same time control the mass output.

A Nebulizer System for Highly Reproducible Aerosol Delivery—M Knoch, E Wunderlich, S Geldner. J Aerosol Med 1994;7:229.

The output characteristics of current nebulizer systems are influenced by factors such as inspiratory flow, temperature and relative humidity of the ambient air, and surface tension of the nebulizing solutions. Due to the resulting alteration of droplet characteristics, the delivery of aerosolized drugs is variable. A nebulizer system, the PARI IS-2, has been designed for the delivery of aerosolized potent drugs. It is characterized by a highly consistent aerosol output and a high proportion of droplet mass in the respirable range. Laboratory testing was performed with a Melvern Particle Sizer and by measurement of total and effective output rates. Preconditioned air was supplied to the system in order to simulate different inspiratory flows (steady state) at varying ambient conditions. There was only a small effect on droplet sizes (MMD 3.0 to 3.6 μm) over the investigated range of inspiratory flow, ambient conditions, and drug solutions. Total and effective output rates of the nebulizer were found to be linearly proportional between 5 and 20 L/min inspiratory flow, thereby compensating for the dilution of aerosol by entrained air. Total output, at a relative humidity between 20% and 80% and at fixed inspiratory flow, varied only by $\pm 6\%$ with respect to 50% relative humidity. The proportion of the dose delivered from the system ranged from 28% to 67% for an initial fill volume between 0.5 and 3 mL, respectively. Thus, for standardized breathing and by using the manual interrupter for on-command therapy, a highly effective delivery and deposition of therapeutic aerosols in the lungs may be achieved with the PARI IS-2 nebulizer system. Due to the small droplet sizes (80% of the mass below 5 μm), side effects caused by aerosol deposition in the mouth and oropharynx are expected to be reduced to a minimum.

Pressure-Volume Relations of the Respiratory System in Healthy Children—A Thorsteinsson, A Larsson, C Jonmarker, O Werner. Am J Respir Crit Care Med 1994;150:421.

Static pressure-volume (P-V) curves of the respiratory system were obtained in 48 healthy children (1 mo to 16 yr of age) during anesthesia and muscle paralysis. The lungs were inflated to a pressure of 25 to 40 cm H_2O, and during the subsequent deflation an interrupter placed in the airway tubing opened and closed every 0.16 s. Airway flow was integrated to obtain the volume decrement between consecutive flow interruptions. Airway pressure was measured during interruptions, and a curve relating pressure to lung volume was plotted, assuming the lung volume at zero pressure to equal functional residual capacity (FRC). FRC was measured using tracer gas washout. The maximum slope of the P-V curve (maximum compliance = C_{rs}max, mL/cm H_2O) was closely related to length (in centimeters) of the child: $C_{rs}max = 7.7 \times 10^{-4} \times length^{2.38}$; $r = 0.97$. The pressure coinciding with C_{rs}max was 6 ± 1 cm

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H_2O (mean ± SD) in infants (1 to 6 mo of age) and 12 ± 1 cm H_2O in older children (> 1.5 yr of age). Total lung capacity (TLC) per kg body weight increased with age and was 52 ± 13 mL/kg in infants and 87 ± 11 mL/kg in older children. The FRC/TLC ratio was greater in infants (38 ± 4%) than in older children (30 ± 5%). The lung volume coinciding with C_{rs}max was nearly the same at all ages, when expressed as a percentage of TLC: 62 ± 3%. Specific compliance of the respiratory system, that is, C_{rs}max/TLC, decreased with growth and was 0.044 ± 0.006 cm H_2O^{-1} in infants and 0.035 ± 0.004 cm H_2O^{-1} in older children. It is concluded that although the P-V relations of the respiratory system changed markedly with growth, especially during the first year of life, the lung volume (%TLC) at which maximum compliance occurred varied little.

Reduction in Lung Injury after Combined Surfactant and High-Frequency Ventilation—JC Jackson, WE Truog, TA Standaert, JH Murphy, SE Juul, EY Chi, J Hildebrandt, WA Hodson. Am J Respir Crit Care Med 1994;150:534.

Previous studies demonstrated that high-frequency oscillatory ventilation (HFOV) begun at birth limits the development of alveolar proteinaceous edema in premature monkeys at risk for hyaline membrane disease (HMD). We hypothesized that exogenous surfactant combined with HFOV would lead to even further reductions in edema. Twenty *Macaca nemestrina* monkeys were delivered at 134 d gestation (term = 168 d) and treated with either HFOV or conventional mechanical ventilation (CMV) from the first breath; modified bovine surfactant (Survanta® [beractant]) was introduced into the trachea over the first few minutes of life. These animals were compared with 20 animals treated with either CMV or HFOV but without surfactant. At 6 h the lung was rapidly frozen in situ during inflation for determination of the volume fraction of alveolar edema. The combined use of surfactant and HFOV from the first breath reduced alveolar proteinaceous edema (3 ± 1%; mean ± SEM) from that seen with CMV alone (27 ± 3%, $p < 0.0001$), CMV after surfactant (21 ± 3%, $p < 0.0001$), and HFOV alone (13 ± 3%, $p < 0.015$). We conclude that the use of surfactant with HFOV after premature birth is superior to either surfactant or HFOV alone in reducing lung injury during the first few hours of life. We speculate that this reduction in lung injury may reduce the incidence or severity of bronchopulmonary dysplasia.

The Respiratory Health Impact of a Large Urban Fire—M Lipsett, K Waller, D Shusterman, S Thollaug, W Brunner. Am J Public Health 1994;84:434.

OBJECTIVES: In July 1988, a fire destroyed a huge supermarket warehouse in Richmond, Calif, sending smoke into residential neighborhoods for nearly a week. There was no organized public health response. To evaluate the respiratory health impact on the general population, a survey of emergency room visits and hospital admissions to the two acute-care hospitals serving the population downwind was conducted. METHODS: Medical records of 489 patients meeting specified diagnostic criteria during the week of the fire and several reference periods were abstracted. Ratios of proportions for respiratory diagnoses (ie, emergency room visits for a given diagnosis/total emergency room visits) were calculated comparing the fire week with the reference periods, and 1988 mortality data for the area were reviewed. RESULTS: Ratios of proportions for emergency room visits for asthma and all lower respiratory conditions increased significantly during the fire. Respiratory-related hospitalizations also increased. However, there was no observable increase in respiratory mortality. CONCLUSIONS: This fire was found to have had a moderate impact on the respiratory health of local residents. Public health intervention is indicated to prevent respiratory morbidity when extended exposure to structural fire smoke is predictable.

Smokeless Tobacco Use and Increased Cardiovascular Mortality among Swedish Construction Workers—G Bolinder, L Alfredsson, A Englund, U de Faire. Am J Public Health 1994;84:399.

OBJECTIVES: Little is known about the risks of cardiovascular disease associated with the use of smokeless tobacco, which produces blood nicotine levels similar to those caused by cigarette smoking. METHODS: Male Swedish construction industry employees (n = 135 036) who attended a health examination were followed by studying cause-specific mortality during a 12-year period. The study population comprised 6297 smokeless tobacco users, 14 983 smokers of fewer than 15 cigarettes per day, 13 518 smokers of 15 or more cigarettes per day, 17 437 ex-smokers, 50 255 "other" tobacco users, and 32 546 nonusers. RESULTS: The age-adjusted relative risk of dying from cardiovascular disease was 1.4 for smokeless tobacco users and 1.9 for smokers of 15 or more cigarettes per day, compared with nonusers. Among men aged 35 through 54 years at the start of follow-up, the relative risk was 2.1 for smokeless tobacco users and 3.2 for smokers. When data were adjusted for body mass index, blood pressure, and history of heart symptoms, the results were essentially unchanged. Cancer mortality was not raised in smokeless tobacco users. CONCLUSIONS: Both smokeless tobacco users and smokers face a higher risk of dying from cardiovascular disease than nonusers. Although the risk is lower for smokeless tobacco users than for smokers, the excess risk gives cause for preventive actions.

The Report of the Surgeon General: Preventing Tobacco Use among Young People—MJ Elders, CL Perry, MP Erikson, GA Giovino. Am J Public Health 1994;84:543.

This year's surgeon general's report on smoking and health is the first such report to focus on young people. From extensive data that indicate that tobacco use is a pediatric epidemic, the report reached six major conclusions: (1) Nearly all first use of tobacco occurs by age 18. (2) Most adolescent smokers are addicted to nicotine. (3) Tobacco is often the first drug used by young people who subsequently use illegal drugs. (4) There are identified psychosocial factors for the onset of tobacco use. (5) Cigarette advertising also appears to increase young people's risk of smoking. (6) Communitywide efforts have successfully reduced adolescent use of tobacco. This commentary restates each of the six conclusions, summarizes the data that support each, and then considers the implications of the conclusions for public health action.

Tobacco Use by Black and White Adolescents: The Validity of Self-Reports—KE Bauman, SE Ennett. Am J Public Health 1994;84:394.

OBJECTIVES: Previous studies concluded that Black adolescents use tobacco and other drugs less than White adolescents. The Black-White differences typically were attributed to variations in background and life-style. The objective of the research reported in this paper was to determine whether the presumed difference in tobacco use is due to Black-White differences in the validity of self-reports. METHODS: We used biochemical measures to compare the validity of self-reports of tobacco use by 1823 Black and White adolescents and to assess the contribution of variation in validity to Black-White differences in reported tobacco use. RESULTS: The sensitivity of Blacks' reports was significantly less than the sensitivity of Whites' reports. The specificity of Whites' reports was significantly less than the specificity of Blacks' reports. Much of the Black-White differences in reports of cigarette smoking and tobacco use were due to Black-White differences in validity. CONCLUSIONS: Studies of Black-White differences should adjust for the invalidity of reports or acknowledge that much of the difference may be due to measurement error.

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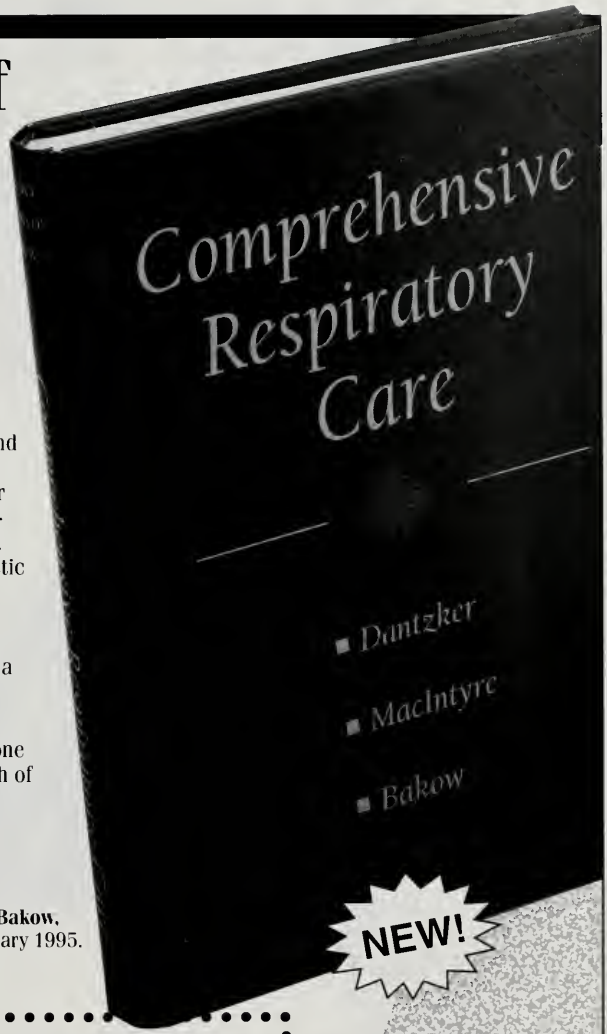

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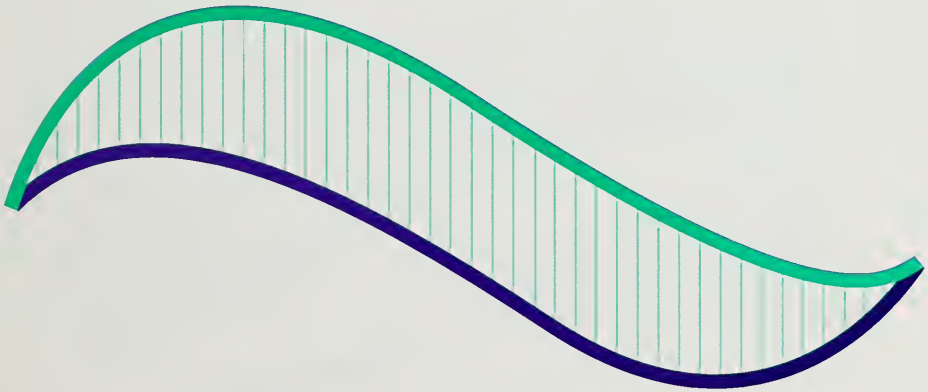

Working Together for Added FEV_1 in COPD

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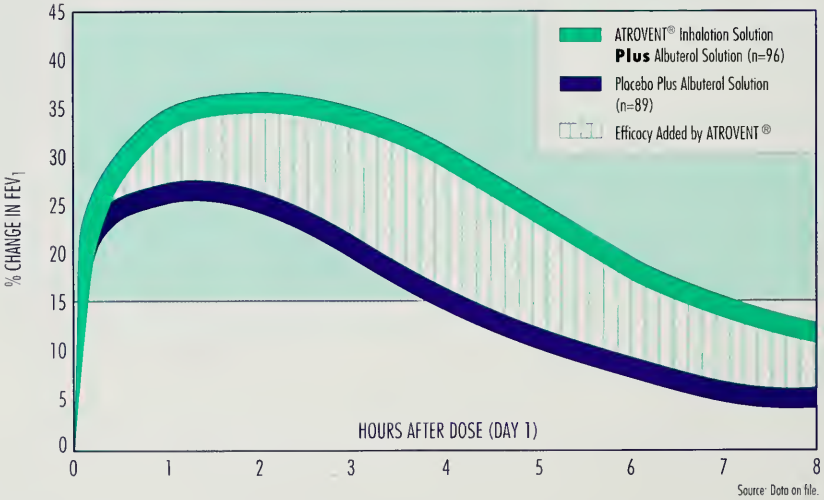
In combination with albuterol



Source: Data on file.

In patients with COPD, ATROVENT Inhalation Solution plus albuterol solution produced significantly greater improvement in FEV_1 than albuterol alone.[1*]

ATROVENT Inhalation Solution is a bronchodilator for the maintenance treatment of bronchospasm in COPD.

* Multicenter, randomized, double-blind, parallel trial conducted in 195 patients with COPD in whom pretreatment mean FEV_1 = 39% of predicted normal.

Please see brief summary of Prescribing Information on last page of this advertisement.

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. . .without lowering the safety profile

The combination of ATROVENT Inhalation Solution and albuterol solution produced no clinically significant increase in side effects compared with albuterol alone.[2]

ATROVENT Inhalation Solution has a low incidence of systemic anticholinergic side effects.[3]

The use of ATROVENT Inhalation Solution as a single agent for the relief of bronchospasm in acute COPD exacerbation has not been adequately studied. Drugs with faster onset of action may be preferable as initial therapy in this situation.

Combination of ATROVENT and beta agonists has not been shown to be more effective than either drug alone in reversing the bronchospasm associated with acute COPD exacerbation.

ATROVENT should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Please see Prescribing Information for all adverse events, regardless of drug relationship, reported in the 12-week controlled trials of ATROVENT Inhalation Solution.

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ADDED EFFICACY WITHOUT ADDED SIDE EFFECTS*

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Brief Summary of Prescribing Information

CONTRAINDICATIONS Atrovent® (ipratropium bromide) is contraindicated in known or suspected cases of hypersensitivity to ipratropium bromide, or to atropine and its derivatives.

WARNINGS The use of Atrovent® (ipratropium bromide) Inhalation Solution as a single agent for the relief of bronchospasm in acute COPD exacerbation has not been adequately studied. Drugs with faster onset of action may be preferable as initial therapy in this situation. Combination of Atrovent and beta agonists has not been shown to be more effective than either drug alone in reversing the bronchospasm associated with acute COPD exacerbation.

PRECAUTIONS General Atrovent® (ipratropium bromide) should be used with caution in patients with narrow angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Information for Patients Patients should be advised that temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain may result if the solution comes into direct contact with the eyes. Use of a nebulizer with mouthpiece rather than face mask may be preferable, to reduce the likelihood of the nebulizer solution reaching the eyes. Patients should be advised that Atrovent Inhalation Solution can be mixed in the nebulizer with albuterol if used within one hour. Compatibility data are not currently available with other drugs. Patients should be reminded that Atrovent Inhalation Solution should be used consistently as prescribed throughout the course of therapy.

Drug Interactions Atrovent has been shown to be a safe and effective bronchodilator when used in conjunction with beta adrenergic bronchodilators. Atrovent has also been used with other pulmonary medications, including methylxanthines and corticosteroids, without adverse drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at dietary doses up to 6 mg/kg/day of Atrovent. Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative. Fertility of male or female rats at oral doses up to 50 mg/kg/day was unaffected by Atrovent administration. At doses above 90 mg/kg, increased resorption and decreased conception rates were observed.

Pregnancy *TERATOGENIC EFFECTS. Pregnancy Category B.* Oral reproduction studies performed in mice, rats and rabbits at doses of 10, 100, and 125 mg/kg respectively, and inhalation reproduction studies in rats and rabbits at doses of 1.5 and 1.8 mg/kg (or approximately 38 and 45 times the recommended human daily dose) respectively, have demonstrated no evidence of teratogenic effects as a result of Atrovent. However, no adequate or well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, Atrovent should be used during pregnancy only if clearly needed.

Nursing Mothers It is not known whether Atrovent is excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that Atrovent® (ipratropium bromide) would reach the infant to a significant extent, especially when taken by inhalation, since Atrovent is not well absorbed systemically after inhalation or oral administration. However, because many drugs are excreted in human milk, caution should be exercised when Atrovent is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS Adverse reaction information concerning Atrovent® (ipratropium bromide) Inhalation Solution is derived from 12-week active-controlled clinical trials. Additional information is derived from foreign post-marketing experience and the published literature.

All adverse events, regardless of drug relationship, reported by three percent or more patients in the 12-week controlled clinical trials appear in the table below.

All Adverse Events, from Double-blind, Parallel, 12-week Studies of Patients with COPD*

	PERCENT OF PATIENTS				
	Atrovent® (500 mcg t.i.d) n=219	**Alupent®** (15 mg t.i.d) n=212	**Atrovent®/Alupent®** (500 mcg t.i.d/ 15 mg t.i.d) n=108	**Albuterol** (2.5 mg t.i.d) n=205	**Atrovent®/Albuterol** (500 mcg t.i.d/ 2.5 mg t.i.d) n=100
Body as a Whole-General Disorders					
Headache	6.4	5.2	6.5	6.3	9.0
Pain	4.1	3.3	0.9	2.9	5.0
Influenza-like symptoms	3.7	4.7	6.5	0.5	1.0
Back pain	3.2	1.9	1.9	2.4	0.0
Chest pain	3.2	4.2	5.6	2.0	1.0

All Adverse Events, from Double-blind, Parallel, 12-week Studies of Patients with COPD*

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Cardiovascular Disorders					
Hypertension/ Hypertension Aggravated	0.9	1.9	0.9	1.5	4.0
Central & Peripheral Nervous System					
Dizziness	2.3	3.3	1.9	3.9	4.0
Insomnia	0.9	0.5	4.6	1.0	1.0
Tremor	0.9	7.1	8.3	1.0	0.0
Nervousness	0.5	4.7	6.5	1.0	1.0
Gastrointestinal System Disorders					
Mouth Dryness	3.2	0.0	1.9	2.0	3.0
Nausea	4.1	3.8	1.9	2.9	2.0
Constipation	0.9	0.0	3.7	1.0	1.0
Musculo-skeletal System Disorders					
Arthritis	0.9	1.4	0.9	0.5	3.0
Respiratory System Disorders (Lower)					
Coughing	4.6	8.0	6.5	5.4	6.0
Dyspnea	9.6	13.2	16.7	12.7	9.0
Bronchitis	14.6	24.5	15.7	16.6	20.0
Bronchospasm	2.3	2.8	4.6	5.4	5.0
Sputum Increased	1.4	1.4	4.6	3.4	0.0
Respiratory Disorder	0.0	6.1	6.5	2.0	4.0
Respiratory System Disorders (Upper)					
Upper Respiratory Tract Infection	13.2	11.3	9.3	12.2	16.0
Pharyngitis	3.7	4.2	5.6	2.9	4.0
Rhinitis	2.3	4.2	1.9	2.4	0.0
Sinusitis	2.3	2.8	0.9	5.4	4.0

*All adverse events, regardless of drug relationship, reported by three percent or more patients in the 12-week controlled clinical trials.

Additional adverse reactions reported in less than three percent of the patients treated with Atrovent include tachycardia, palpitations, eye pain, urinary retention, urinary tract infection and urticaria. A single case of anaphylaxis thought to be possibly related to Atrovent has been reported. Cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported.

Lower respiratory adverse reactions (bronchitis, dyspnea and bronchospasm) were the most common events leading to discontinuation of Atrovent therapy in the 12-week trials. Headache, mouth dryness and aggravation of COPD symptoms are more common when the total daily dose of Atrovent equals or exceeds 2,000 mcg.

HOW SUPPLIED Atrovent® (ipratropium bromide) Inhalation Solution Unit-Dose Vial is supplied as a 0.02% clear, colorless solution containing 2.5 ml with 25 vials per foil pouch (NDC 0597-0080-62). Each vial is made from a low density polyethylene (LDPE) resin.

Consult package insert before prescribing.

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* When used in combination with a beta-agonist solution, ATROVENT does not significantly increase side effects associated with the beta agonist alone.

References: 1. Levin DC, Little KS, Laughlin KR, Galbraith JM. Ipratropium bromide solution in COPD augments extent and duration of FEV_1 increases achieved by albuterol up to 85 days. *Chest.* 1993;104(suppl to No. 2):112S. Abstract. **2.** Data on file, Boehringer Ingelheim Pharmaceuticals, Inc. **3.** ATROVENT® (ipratropium bromide) Inhalation Solution full Prescribing Information.

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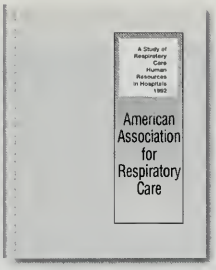
The AARC Human Resources Survey: A Study of Respiratory Care Human Resources in Hospitals



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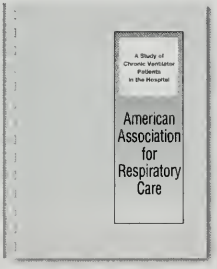

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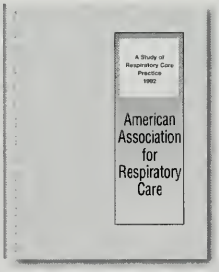

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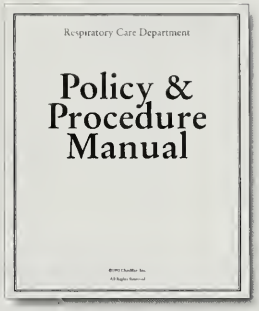

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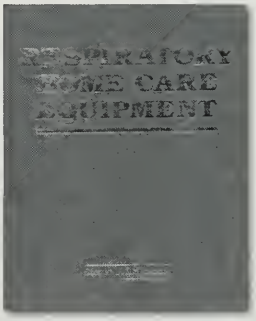

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CPGs 1994: Where Are We? Where Have We Been? Where Are We Going?

After more than 4 years of concerted effort by Focus Groups, the Steering Committee, outside resource persons, and reviewers, it's time for an update on AARC Clinical Practice Guidelines (CPG) activity. Indeed, where are we? Where have we been? Where are we going?

Where Are We?

With the four Guidelines published in this issue of the Journal—addressing transcutaneous monitoring,[1] capillary blood gas sampling,[2] body plethysmography,[3] and indirect calorimetry[4]—the total number of approved and published Guidelines reaches 33.[5-9]

Those Guidelines have helped establish therapist-driven protocols, found their way into policy and procedure manuals, provided indicators for quality improvement (CQI), supported the expanded role of the respiratory care practitioner, and caught the attention of the respiratory care community worldwide (Fig. 1).

The Association has distributed more than 15,000 reprints of the Guidelines (in addition to their publication in the Journal) and has further fostered dissemination by permitting and encouraging photocopying for purposes of training and utilization.

With many basic procedures addressed and some remaining to be completed, the Guideline emphasis is changing, some of the players have retired, and we will be moving farther afield, but the philosophy, intent, and format stand polished and, perhaps while not 'perfected,' certainly enduring and true to the Association's original purpose.[10]

Where Have We Been?

The Guideline effort—after months, perhaps years, of thought and planning—was launched in 1990 by then AARC president Jerome Sullivan. The Steering Committee was selected[10] and Dean Hess was chosen to head up the undertaking. Dean devised and proposed the basic framework for the Guidelines.[10] The operational mode was established—an exhaustive search, recovery, and analysis of the literature would provide the launch pad for each Guideline, input from clinicians and content specialists would set the course, and outside review would assure that the Guideline was on target. Focus Groups were appointed and charged. The Review Panel of 650 reviewers was assembled. The first year was one of intense effort, with some stops and starts and faltering—the necessary 'shakedown cruise' for each of the Focus Groups—but that effort paid off with the publication of the first Guidelines in December 1991.[5] Each year has seen continued intense effort and the publication of additional Guidelines.

Where Are We Going?

July 1995 will see the publication of Guidelines addressing emergency airway management, respiratory muscle training and breathing exercises, exercise testing with expired gas analysis, sleep apnea, infant-toddler pulmonary functions testing, delivery of aerosol to the lung parenchyma, assessment of bronchodilator response, patient-therapist education, neonatal transport, and delivery room resuscitation.

Guidelines under development for later publication include mechanical ventilation in the home, pressure-limited ventilation, high frequency oscillatory ventilation for the neonate and infant, intubation/extubation, and patient assessment prior to and during weaning.

Each Focus Group member maintains an ongoing awareness of the need for revision of specific Guidelines—collecting pertinent papers and pertinent comments and observations from clinicians.

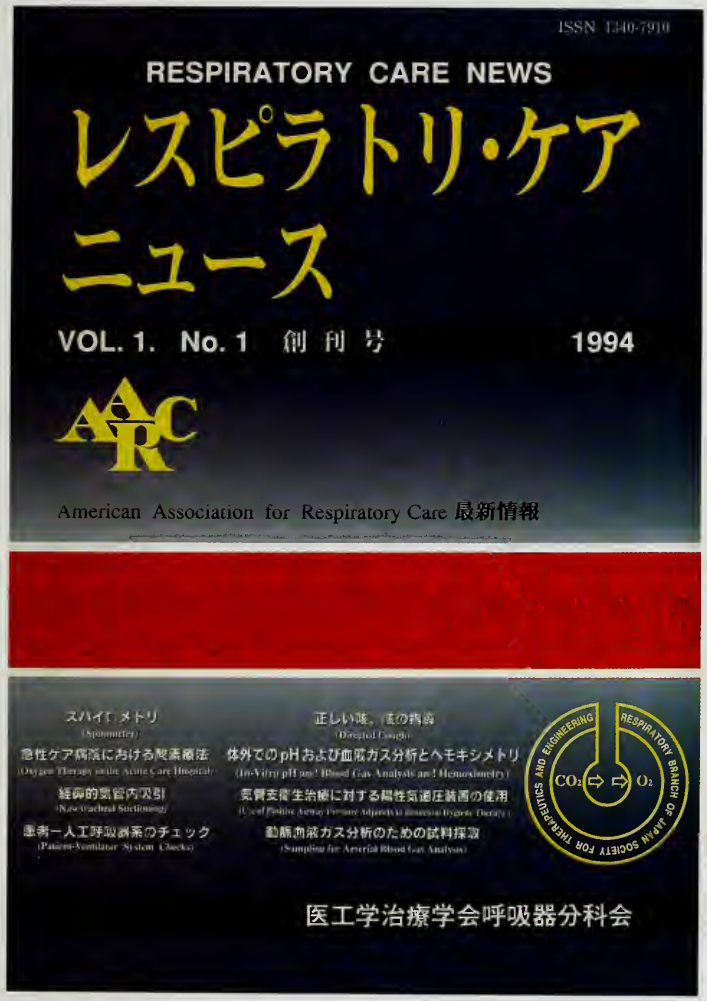

Fig. 1 AARC Clinical Practice Guidelines are being adopted abroad as well as in the U.S. The Japanese publication *Respiratory Care News* is shown.

Where does the 'average' clinician-therapist-practitioner-educator fit into the CPG effort? The CPG Steering Committee needs (1) your formal critique (via your participation on the Review Panel—just send your name and address to Joy Rea, 11030 Ables Ln, Dallas TX 75229), (2) your informal critique (positive or negative, by phone, fax, letter, or face-to-face), (3) your suggestions for future Guidelines, and (4) your account of how you and your department or program use the Guidelines.

The AARC remains committed to the task and the concept as do the Steering Committee, Focus Group members, and reviewers. Put CPG involvement at some level on your "To-Do" list for 1995!

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Guideline for Prevention of Nosocomial Pneumonia and Ventilator Circuits: Time for Change?

In this issue of RESPIRATORY CARE, the new CDC *Guideline for Prevention of Nosocomial Pneumonia* is published.[1] It is long overdue, with the previous guideline published in 1983.[2] Physicians, respiratory care practitioners, and nurses responsible for the respiratory care of patients should find this guideline useful. In addition to the Guideline, a current review of the literature (over 700 references) related to issues on prevention of nosocomial pneumonia is provided.

Many respiratory care practitioners have anxiously awaited this Guideline for more contemporary recommendations regarding ventilator-circuit change frequency. Previous guidelines suggested daily ventilator-circuit changes. However, studies published since those guidelines resulted in the common practice of changing circuits every 48 hours.[3,4] More recently, evidence has emerged suggesting that ventilator circuits may not need to be changed at all.[5] The issue of ventilator-circuit-change frequency is currently a hot topic—there were six OPEN FORUM abstracts presented at this year's AARC meeting on this subject.[6-11]

I suspect that many respiratory care practitioners will be disappointed with the new CDC recommendations for ventilator-circuit-change frequency:

> Do not routinely change more frequently than every 48 hours the breathing circuit, including tubing and exhalation valve, and the attached bubbling or wick humidifier of a ventilator that is in use on an individual patient. No recommendation for maximum length of time after which the breathing circuit and the attached bubbling or wick humidifier of a ventilator in use on a patient should be changed.[1]

What does this mean? Why didn't the CDC take a stronger stand on this issue? How does this help me convince my Infection Control Department to allow circuits to be changed once per week?

In reality, there is not strong evidence in the literature for infrequent ventilator-circuit changes (eg, change intervals longer than 48 hours). There are too few good studies in the peer-reviewed literature to make a stronger recommendation on this issue. The Guideline is worded in a manner that allows less frequent circuit changes but places the responsibility on the hospital to determine the specific ventilator-circuit-change frequency beyond 48 hours.

I personally believe that strong circumstantial evidence supports weekly circuit changes (and perhaps even less frequent than that). I also believe that respiratory care practitioners can work with infection control practitioners to design infection control surveillance programs that provide institution-specific data to support less frequent circuit changes. We did that at the Massachusetts General Hospital—and it resulted in our weekly circuit-change policy.

Why Infrequent Circuit Changes?

Changing ventilator circuits is not a benign procedure. Circuits are changed on ventilators attached to the most critically ill patients in the hospital. The incidence of serious incidents occurring during ventilator-circuit changes is unknown and is probably under-reported. I am certain that circuits are changed on ventilators attached to patients for whom the risk of injury related to the circuit change is greater than the risk of pneumonia if the circuit were not changed. I am sure that many respiratory care practitioners (myself included) have made the clandestine decision not to change a ventilator circuit for a critically ill patient due to fear of an adverse event during the circuit change.

Frequent changing of ventilator circuits is expensive, both in terms of materials and personnel time. At the Massachusetts General Hospital, we realized a materials cost reduction of nearly $40,000 per year with weekly ventilator circuit changes (as compared to 48-hour circuit changes). Further, about 1,330 hours of personnel time (> 0.5 full-time-equivalent) were saved. These savings become increasingly important in the current era of personnel downsizing and shrinking budgets. It is critical for us, as respiratory care practioners, to identify areas where savings can be realized—allowing us to concentrate time and resources on other important areas. For example, I would much rather see the respiratory therapist have time to interact with physicians about a patient's ventilator management than to spend that time performing an unnecessary task.

In the acute care setting, most of the cost savings are realized by extending the ventilator-circuit-change frequen-

cy to every 7 days. At the Massachusetts General Hospital, more than 80% of patients are ventilated for less than 1 week. Thus, fewer than 20% of ventilated patients ever have their circuits changed.

What is the Evidence?

The two most important routes of bacterial invasion of the lower respiratory tract are aspiration of oropharyngeal secretions and inhalation of aerosols containing bacteria.[1] Current evidence strongly supports aspiration as the most important cause of nosocomial pneumonia. It is now recognized that cuffed endotracheal tubes do not prevent aspiration of oropharyngeal secretions. From my review of the literature on this subject,[12] I have become strongly convinced that nosocomial pneumonia in intubated mechanically ventilated patients is more likely to result from what is aspirated around the endotracheal tube than from what is breathed through the endotracheal tube. If this hypothesis is correct, then the frequency of ventilator circuit changes should have little impact on ventilator-associated pneumonia rates, provided that reasonable infection control practices are followed. As stated by Reinarz et al in 1965, "respirators without mainstream reservoir nebulizers impose no greater risk to a patient than that imposed by breathing room air."[13]

Lareau et al[14] compared ventilator-associated pneumonia rates with circuit-change intervals of 8, 16, and 24 hours. They found no difference in pneumonia rates at these three intervals. Although they did not study circuit changes greater than 24 hours, their study was important because it suggested that frequent circuit changes do not decrease the risk of ventilator-associated pneumonia.

Craven et al,[3] in a frequently cited paper, compared the incidence of ventilator-circuit contamination in 44 patients for whom circuits were changed every 24 hours and in 51 patients for whom circuits were changed every 48 hours. There are several important findings of this study. First, no significant difference in circuit colonization was seen between the two groups. Second, contaminants in the circuits originated from respiratory tracts of the patients—in other words, the patient contaminated the circuit, and not vice versa! Third, water in virtually all Cascade-type humidifiers remained sterile, in spite of heavy contamination of the circuit near the patient. Based upon the results of this study, it became common practice to change ventilator circuits every 48 hours, as opposed to every 24 hours. However, it is important to recognize that this study did not evaluate pneumonia rates. It only measured circuit colonization.

Craven et al[15] may have been the first to evaluate risk factors for nosocomial pneumonia using multivariate statistical techniques. Among those factors found to be significantly associated with the development of ventilator-associated pneumonia, the odds ratio was 2.3 if circuits were changed at 24-hour intervals rather than 48-hour intervals. In other words, the risk of ventilator-associated pneumonia was actually greater if circuits were changed more frequently!

Perhaps the most scientifically rigorous study to evaluate the effects of circuit-change frequency on ventilator-associated pneumonia rates was conducted by Dreyfuss et al.[5] They compared 48-hour circuit changes with no circuit changes. This was a 1-year study in which 35 patients were randomized to have their circuits changed every 48 hours, and 28 patients were randomized to never have their circuits changed. Pneumonia was precisely diagnosed using invasive procedures. Between groups, there was a similar pneumonia rate (31.4% in the circuit-change group, 28.5% in the no-circuit-change group, $p = 0.8$), duration of mechanical ventilation (5-25 days with circuit changes, 5-14 days with no circuit changes, $p = 0.7$), and mortality (8.6% with circuit changes, 7.1% with no circuit changes, $p = 0.8$). Bacterial colonization of the circuit usually followed colonization of the pharynx and trachea, and colonization of water in the humidifier was rare (heated Cascade-type humidifiers were used).

Several studies conducted at the Massachusetts General Hospital evaluated circuit contamination and circuit-change frequency in neonates.[16,17] Based upon the results of these studies, we adopted the practice of changing circuits only between patients (circuits are not routinely changed on mechanically ventilated patients in our neonatal ICU). More recently, we compared ventilator-associated pneumonia rates for adult patients in whom circuits were either changed at 48-hour or 7-day intervals.[6,12] In this study including over 3,000 patients and more than 18,000 ventilator days, no significant difference was seen in ventilator-associated pneumonia rates (the pneumonia rate was actually a bit lower with 7-day circuit changes). Based upon these results, we adopted the practice of weekly circuit changes in adult mechanically ventilated patients at the Massachusetts General Hospital.

Unresolved Issues

There are a number of unresolved issues related to ventilator-circuit-change interval, and I briefly summarize each of these.

Cascade-Type vs Wick Humidifiers

Cascade-type humidifiers bubble gas through water, and the bursting bubble effect of these humidifiers can produce microaerosols. Wick humidifiers, on the other hand, humidify gas by passing it over a water-saturated wick. Rhame et al,[18] in an in-vitro study, showed that

Cascade-type humidifiers produce microaerosols that can carry bacteria. However, the study had two major flaws. None of the humidifiers was heated, and tubing from the humidifier was only 20 cm in length—unlikely conditions during mechanical ventilation of adults. Goularte et al[19] found that the high temperature in the reservoir of Cascade-type humidifiers is bactericidal for nosocomial pathogens. Because colonization of in-use Cascade-type humidifiers is low, microaerosols produced by Cascade-type humidifiers are unlikely sources of ventilator-associated pneumonia.

Several studies have suggested that ventilator-circuit-change intervals can be extended, even with the use of Cascade-type humidifiers.[5,12] I do not believe that there is sufficient evidence to suggest that wick humidifiers are superior to Cascade-type humidifiers relative to the risk for ventilator-associated pneumonia.

Heated vs Unheated Circuits

Heated circuits are used to minimize condensation in ventilator circuits. However, circuit contamination almost always arises from the patient.[3,20] Thus, it might be argued that protecting the patient from ventilator condensate does nothing more than protect the patient from himself. Certainly it is reasonable (and appropriate) to use in-line water traps to aseptically evacuate circuit condensate at regular intervals and to avoid bolus lavage of the patient with circuit condensate. Circuit condensate may contaminate the caregiver and other patients in the same unit, and dealing with circuit condensate can be an inconvenience. However, it is not clear that circuit condensate increases the risk for ventilator-associated pneumonia—particularly if care is taken to remove it periodically.

To my knowledge, no scientific evidence confirms that heated circuits reduce the incidence of ventilator-associated pneumonia. Heated circuits may be convenient for caregivers but may put patients at risk for airway occlusion due to inadequate humidification.[21,22] If heated circuits are used, care must be taken to assure that the patient's inspired gases are adequately humidified. When heated circuits are used the temperature of the humidifier reservoir does not need to be as great, and one might speculate that this could result in growth of pathogens within the humidifier reservoir. It is not known whether this occurs or whether there are any clinical consequences if it does occur.

Open vs Closed-Feed Systems

It is reasonable to expect that a closed-feed humidification system should decrease the contamination of the humidifier reservoir. However, as I stated previously, the temperature within the humidifier reservoir may be bactericidal for respiratory pathogens. Daschner et al[23] found that the use of a closed-feed humidification system did not affect the ventilator-associated pneumonia rate.

Artificial Nose vs Active Humidification

Because artificial noses trap the patient's exhaled humidity, the ventilator circuit remains dry. Some artificial noses also serve as filters. Thus, artificial noses should decrease circuit contamination. However, circuit contamination usually comes from the patient. Is our goal to protect the circuit from the patient? It is unclear whether the use of artificial noses reduces the risk of ventilator-associated pneumonia. To my knowledge no prospective randomized trial of heated humidifiers vs artificial noses of sufficient sample size (ie, adequate statistical power) has answered this question. Although concern remains about the effectiveness of these devices as humidifiers, artificial noses probably can be used safely with proper patient selection.[24]

In-Line Nebulizers

Craven et al[25] have shown that medication nebulizers used in-line during mechanical ventilation are frequently contaminated. Because these produce aerosols that can be delivered into the lower respiratory tract, they are a potential cause of ventilator-associated pneumonia The metered-dose inhaler can be used to deliver aerosolized medications into the ventilator circuit without opening the system. I have suggested that use of metered-dose inhalers has a lower risk for ventilator-associated pneumonia than nebulizers,[26] but this has not been scientifically investigated.

Bag-Valve Resuscitators

Several studies[27,28] have shown that bag-valve resuscitators at the bedside of mechanically ventilated patients are frequently contaminated. These devices should be changed at regular intervals, but the appropriate interval is not known. Although its effectiveness is unproven, our practice is to cap the patient connection of the resuscitator when it is not in use; the same cap is placed on the ventilator Y-piece when the ventilator is removed from the patient.

Open vs Closed Suction

Whether closed suction systems lower the incidence of nosocomial pneumonia is currently unclear. Deppe et al[29] found that the incidence of ventilator-associated pneumonia was similar in groups of patients randomized to open suction (29%) or closed suction (26%). It may be reason-

able to use these devices in patients who already have a pneumonia to prevent spraying of ventilator circuit condensate and tracheal secretions into the environment of the ICU during suctioning.

Acute Care vs Long-Term Care Settings

Most studies of ventilator-associated pneumonia have been conducted in the acute care setting and, usually, in a critical care setting. We need to learn more about the risk factors for pneumonia in patients ventilated outside the ICU. We also need studies to determine how frequently ventilator circuits should be changed in such settings.

Diagnosis of Ventilator-Associated Pneumonia

The diagnosis of pneumonia in ventilated patients is difficult. Traditionally, the diagnosis has been based on clinical indicators such as new or persistent infiltrate and purulent sputum.[30] Recently, invasive bronchoscopic quantitative methods (eg, protected specimen brush and bronochoalveolar lavage) have been used to more precisely diagnose pneumonia in mechanically ventilated patients. However, these methods are not without disadvantages—they are invasive, expensive, and may be less useful in patients already treated with antibiotics. Several recent papers have urged caution in the use and interpretation of these new diagnostic approaches.[31,32] Further, methods such as quantitative cultures are not available in all hospitals.

I doubt that anyone would suggest the use of invasive techniques for routine infection surveillance. This creates a dilemma for respiratory care practitioners and infection control practitioners conducting hospital epidemiologic studies of ventilator-associated pneumonia. Methods necessary to increase the accuracy of diagnosing ventilator-associated pneumonia cannot be routinely used because they are invasive and expensive, but the results of epidemiologic studies based on clinical criteria will be questioned because of potential inaccuracy of the diagnosis. For infection control purposes, ventilator-associated pneumonia will most frequently be identified based upon clinical criteria. The clinical criteria used should be consistent with the recommendations of the CDC,[30] and a uniform approach should be used by trained clinicians. Almost all past studies of the epidemiology of ventilator-associated pneumonia have been based upon clinical criteria.

Recommendations

Ventilator-associated pneumonia may not be ventilator related. I personally believe that ventilator circuits can be changed at weekly intervals (and perhaps less frequently). I am not particularly bothered that the new CDC Guideline does not say this. I am encouraged that the Guideline allows ventilator-circuit-change intervals greater than 48 hours. I challenge respiratory care practitioners to work together with infection control practitioners to resolve the issues related to ventilator-circuit-change frequency. Having done that, I further challenge all of us to conduct these quality assurance projects in a scientifically rigorous manner, so that the results can be published in the peer-reviewed literature.

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The author has no financial interest in any of the products mentioned or in competing products.

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TB Control Guidelines Deserve Our Attention, Too

The CDC *Guidelines for Preventing the Transmission of Mycobacterium Tuberculosis in Health-Care Facilities, 1994*[1] became effective on October 28, 1994. These Guidelines have been under development for more than a year, and, in November 1993, the AARC guided by then President Diane Lewis and Cheryl Brown, Director of Government Affairs for the AARC, submitted comments, some of which have been incorporated into this final version. AARC concerns centered around the use of protective devices in the hospital and in the home, and the need for specific precautions during bronchoscopy and pentamidine aerosol administration.

The document is being printed in its entirety in the *Morbidity and Mortality Weekly Report (MMWR) Recommendations and Reports*. Instruction for retrieval from the *Federal Register* are as follows: "For copies of the MMWR printing, call CDC's Voice Information System (VIS) at (404) 639-1819 or write the Centers for Disease Control and Prevention (CDC), Information Services, Mailstop E-06, Atlanta GA 30333. An electronic version of the document [is] available via Anonymous FTP from ftp.cdc.gov. Type 'Anonymous' for the user name and your e-mail address for the password. Select the pub directory, then the tbdoc subdirectory. Retrieve the README file for instructions on document viewing and printing."

Managers, administrators, department directors, medical directors, and educators and trainers need to be conversant with the content of these Guidelines and their implications for patient and caregiver protection and respiratory care procedures. Copies of this document and the *Guideline for the Prevention of Nosocomial Pneumonia*[2] (published in this issue of the Journal) belong in every respiratory care department!

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Aerosol Research: How Should We Skin This Cat?

Aerosol therapy continues to play an important role in contemporary medicine and in respiratory care in particular. The number of drugs, other than bronchodilators, that have been studied or proposed for topical delivery to the lungs or upper airways by the aerosol route have increased appreciably over the past few years. Certainly, corticosteroids and antimicrobials, such as pentamidine[1] and ribavirin,[2] immediately come to mind. But other agents, such as aminoglycosides,[3] antiproteases,[4] surfactant,[5] antioxidants,[6] and cyclosporine[7] are receiving their share of attention. At first blush, the recent introduction of an aerosol formulation of genetically-engineered recombinant human deoxyribonuclease (rhDNase) for mucolysis in cystic fibrosis (CF) patients[8] might seem to be the apotheosis of aerosol therapy. But my guess is that the penultimate accolades will be reserved for a simple and reliable aerosol method of delivering copies of normal CF genes to the airway epithelium of ambulatory CF patients. But this will require more than just development of a suitable pharmacologic preparation!

Although aerosol therapy is at least 50 years old, the importance of the delivery system is only now being appreciated. The relative ease with which aerosolized beta agonists are administered and the usually predictable therapeutic response that ensues readily lead to the assumption that aerosol therapy is facile. Yet, it is now well known that the choice of delivery system has a profound effect on the efficiency of drug delivery by the aerosol route. Note that I stress the delivery *system* rather than the small volume nebulizer (SVN) or metered dose inhaler (MDI) itself. A system is composed of interrelated parts, each of which contributes to the uniqueness and function of the whole. Rather than the singular devices as they were originally conceived, the SVN and the MDI are now evolving as components of larger systems.

This assertion is supported by a number of examples. At least two different brands of SVN have been intentionally augmented by directional valves and additional tubing for the express purpose of baffling large particles and creating an aerosol of uniformly smaller particles.[9] This collection of tubing, valves, and nebulizer, used specifically to deliver pentamidine aerosol to the alveolar level, is distinctly a system. The classic MDI, virtually unchanged since its introduction in 1956, has been improved in the last decade by the addition of a reservoir, often known as a spacer. These parts, joined and working in concert with one another, are a system. The addition of an integral pediatric mask to one end of the spacer represents further evolution of that particular system.

Building upon the system concept and apparently borrowing ideas from both of these examples, an SVN utilizing principles of directional flow, baffling, adjustable inspiratory resistance, and a spacer has now been introduced. This device has already undergone limited clinical testing as reported by Mason et al[10] in this issue of RESPIRATORY CARE.

The evolution and increasing complexity of aerosol delivery systems leads to still another issue. Namely, how are these hybrid systems going to be tested, characterized, and reported? Traditional pharmaceutical research has stressed the dose-response or pharmacokinetic approach to evaluating drug therapy. However, this is only a partial approach for evaluating aerosol drug therapy because of the vast number of variables, including variations in delivery systems. Thus, the aerosol test bench should be the first stop in any study that seeks to evaluate the efficiency of a new aerosol delivery device, especially a hybrid device that borrows and combines concepts from a multitude of sources.

The importance of bench studies in aerosol research should not be underestimated. Previous clinical studies conducted in my institution found that disposable plastic nebulizers, even from the same lot, do not always perform comparably.[1,11,12] Thus, when conducting studies involving many nebulizers, we now customarily pretest a sufficient number of devices to ascertain that they all function comparably or to identify and discard outliers from the group that will be used clinically or in further bench tests. This simple but often overlooked procedure can help to ascertain whether aberrant results in a clinical study, for example, are due to system factors or patient factors.

The procedure nicknamed "standing cloud"[12,13] uses an absolute filter to capture all particles that leave the nebulizer as it is run to dryness. Identical amounts of drug or radioactive tracer are placed in a series of nebulizers, and the experiment is repeated for each. Duration of nebulization until dryness and/or the amount of drug or tracer measured on the filter form the

basis for comparability. Simple statistical analysis characterizes like performers and identifies outliers in the sample.

One situation in which the standing-cloud measurement would be valuable is the testing of new aerosol delivery systems that have been created from combining features of others. In the paper by Mason et al[10] in this issue of RESPIRATORY CARE, for example, the standing-cloud measurement would have been useful in determining whether there were any intrinsic differences between the two nebulizers used in the study. The paper makes a comparison between a stand-alone nebulizer of one brand and another brand of nebulizer incorporated into a system. While the results of the study are indeed interesting, the absence of preliminary bench testing raises additional questions.

This should be taken as commentary rather than criticism inasmuch as appropriate testing of new and increasingly complex aerosol delivery systems is itself a new and increasingly complex venture. While unusual for one editorial to point to another, I am compelled to recommend a recent editorial by Smaldone,[13] in the *Journal of Aerosol Medicine*. It explores many facets of the technical issues of aerosol drug delivery and some of the problems investigators are experiencing in utilizing a common language for reporting and describing their work. However, despite these problems, it is clear that a new era is dawning in the field of aerosol drug delivery, and it is accompanied by an awakening recognition of the need for improved assessment of aerosol delivery system function and performance.

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Comparison of Aerosol Delivery via Circulaire System vs Conventional Small Volume Nebulizer

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BACKGROUND: Contemporary small volume nebulizers have the disadvantages of low efficiency, extrapulmonary deposition of medication leading to side effects, and possible environmental contamination. DESCRIPTION OF DEVICE: The Circulaire nebulizer® is mated to a circuit that includes a one-way valve to baffle large particles and direct airflow, a distensible reservoir to capture aerosol from the nebulizer during expiration, and a variable resistor to optimize nebulizer function for the individual patient. EVALUATION METHODS: Performance of 9 units of the new device (nebulizer plus circuit) was compared to performance of 9 conventional nebulizer units by aerosol techniques that permitted quantitation of aerosol deposition. RESULTS: Compared to a conventional nebulizer, the Circulaire system produced a statistically significant improvement ($p < 0.05$) in lung deposition (50% increase), a fivefold reduction in extrapulmonary deposition, and a twofold reduction in amount of aerosol escaping to the environment. CONCLUSION: Our study suggests that the Circulaire system demonstrates (1) improved efficiency of aerosol delivery to the lungs, (2) reduced aerosol deposition in the body outside of the lungs, and (3) less escape of aerosol to the environment when compared to a conventional nebulizer. [Respir Care 1994;39(12):1157-1161.]

Introduction

Among the options for delivery of aerosol therapy, small volume nebulizers are popular and versatile devices, but they are far from perfect. One of the problems is their low efficiency (ie, the small fraction of the fill volume actually deposited in the lungs). Investigators have demonstrated that only 2.7-12.4% of the medication placed in the nebulizer is deposited in the lungs.[1-5] A typical delivery is no more than about 10%. If low efficiency were the only factor, simply increasing the dose might suffice because most aerosol medication is relatively inexpensive. Unfortunately, conventional small volume nebulizers (SVNs) produce a variety of particle sizes, the larger of which impact the pharynx, are systemically absorbed, and may produce undesirable side effects. The larger particles may be in part removed from the nebulizer output by the use of a spacer and/or one-way valve baffle such as that incorporated into the Respirgard II® nebulizer approved for inhaled pentamidine.[6] Unfortunately, this may lead to even less efficiency—approximately 4-5%.[7-9]

Low efficiency is due in part to the so-called dead volume (ie, the volume of the medication plus diluent remaining in the SVN that cannot be aerosolized) and in large part to the aerosol vented to the atmosphere during the expiratory phase of the respiratory cycle.[10] One solution is to somehow capture the otherwise lost aerosol for subsequent inhalation. We evaluated a new nebulizer design that utilizes a spacer and baffles coupled with a distensible reservoir. Our hypothesis was that compared to a conventional SVN, the Circulaire® nebulizer with its inspiratory circuit (C-system)* would provide equal or greater efficiency while minimizing deposition in the gastrointestinal tract.

An additional concern with conventional SVN therapy is release of aerosol into the environment. Therefore, our second

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*Manufacturers and suppliers are identified in the Product Source section at the end of the text.

hypothesis was that less aerosol would escape into the environment with the C-system.

Description of Device

The C-system is a small volume jet nebulizer mated to a breathing circuit designed to optimize function (Fig. 1). A one-way valve placed between the nebulizer and the patient serves as a baffle to remove many of the larger particles otherwise destined for loss to room air or for pharyngeal deposition in the patient. The one-way valve also directs the nebulizer output to the distensible reservoir during expiration. The reservoir captures the aerosol during expiration and makes it available to the patient on subsequent inspiration. To provide patients with additional air should they inhale beyond the combined volume of the reservoir and the nebulizer output, a port open to ambient air is required. For the device to function properly, this port is provided with an inspiratory retard that may be adjusted so that it is sufficient to overcome the inspiratory resistance of the one-way valve and encourage the patient to breathe preferentially from the nebulizer side of the circuit.

Evaluation Methods

Measurements

In order to quantitate aerosol deposition in the body and elsewhere, it is usually necessary to generate a radioactive aerosol that permits imaging and counting by gamma camera. We employed such techniques in this study.[9]

To provide a standard for comparison, we studied each subject (ie, 9 subjects, 9 units of each device) using both a C-system and an Airlife Misty-Neb (M-neb), which is the small volume nebulizer commonly used in our institution.

The particle size data were obtained with a California Measurements' model PC-2AS 10-stage impactor system. This multistage inertial impaction instrument provided size distribution of the normal saline aerosol within seconds after each sampling run. The instrument encompasses a particle size range of 0.14 to > 10 μ in 10 size fractions and is a low-pressure cascade impactor system operating at a flowrate of 0.24 L/min. Oscillating piezoelectric quartz crystals are used in each impactor stage as 'live' particle mass sensors to provide real-time data. The cascade impactor is connected to the nebulizer mouthpiece for these studies.

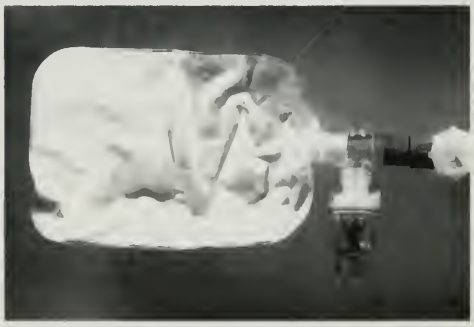

Fig. 1. Photograph of the Circulaire system.

Protocol

Following approval by our Institutional Review Board, we recruited 9 normal subjects who gave informed consent for participation in the study. The subjects were studied on two separate days, on one day with the M-neb and on the other with the C-system. The order of study was randomized by coin toss. Approximately 3 millicuries of 99m technetium diethylenetriamine-penta acetate (DPTA) in 3.5 mL of normal saline solution was added to the nebulizer. On each day, the subject underwent a simulated aerosol treatment seated upright with a nosesclip in place, in front of a gamma camera. To minimize escape of the radioactive aerosol into the environment, subjects were instructed not to remove the mouthpiece during nebulization, and a filter was placed on the nebulizer opening to atmosphere. Subsequent gamma-camera (γ-Cam), or particle, counting of these filters allowed measurement of aerosol that otherwise would have been vented to room air. Treatments were delivered in the conventional fashion with the subject breathing normally and nebulizer flow at 7 L/min from a wall oxygen source. The treatment proceeded to 'dryness' (ie, no further aerosol could be seen leaving the nebulizer even after the device had been tapped). A usual treatment took 6-10 minutes.

Differences in outcome variables (eg, deposition, particle size) were compared between C-system and M-neb using paired *t* tests.

Radioactive Scanning

Measurement of aerosol deposition was achieved by quantitative γ-Cam counting of the radioactivity in the device pretreatment and in regions of interest over the posterior aspect of the body during and after treatment. Results were expressed as the ratio of corrected-to-baseline nebulizer counts. The corrected count in the lung expressed as percent of count initially placed in the nebulizer is designated as % Lung. The corrected counts in the region of interest circumscribing pharynx, stomach, and esophagus as percent of nebulizer counts are designated %GI. Typical deposition images are shown in Figure 2A and 2B.

Correction of lung counts for attenuation of internal radioactivity by body tissues was achieved by measurement of transthoracic attenuation of a known source. The half-value is calculated by assuming a semilogarithmic attenuation of counts over

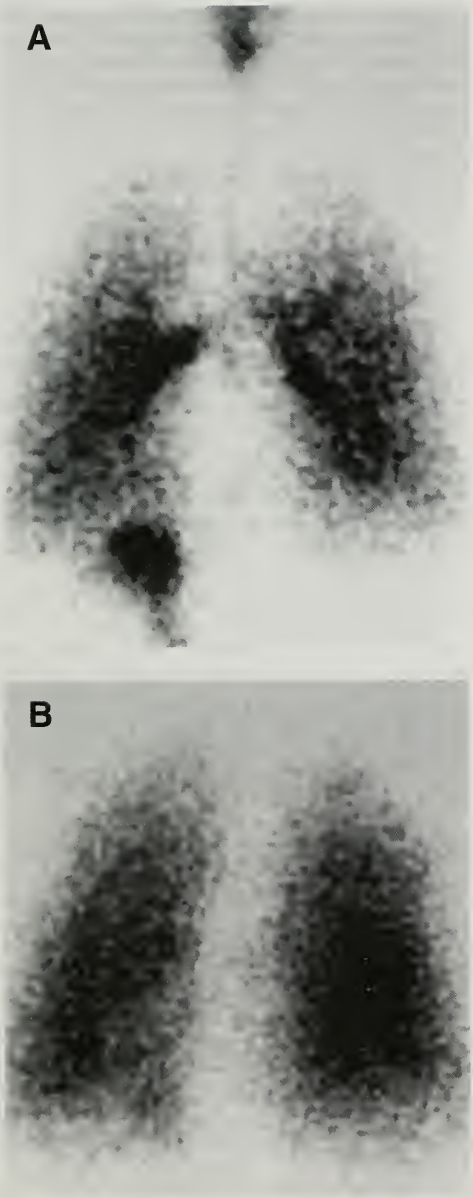

Fig. 2A. Scan of lung following administration of ^{99m}technetium diethylenetriamine-penta acetate (DPTA) via Misty-Neb nebulizer. 2B. Scan following administration of DPTA via Circulaire.

transthoracic distance for each subject. This typically increases counts about twofold.[9,12] In addition, counts were corrected for the physical decay of the isotope and biologic loss of tracer from the lungs through vascular absorption. We measured the rate of absorption and applied minute-by-minute correction for vascular absorption to deposited counts.[9] The total corrected γ-Cam count deposited during nebulization is the sum of these minute-by-minute observations as corrected. In normal subjects, only 0.5-1.0 %/min is typical, and over a nebulization period of a few minutes the correction is of small magnitude. However, in subjects with active alveolitis, the correction may be much larger.[13]

The filters were counted and expressed as the percentage of baseline γ-Cam count placed in the nebulizer to determine the amount of atmospheric contamination (% Room). The nebulizers alone without the circuits were counted and expressed in the same fashion to determine dead volume (% Dead).

Aerosol penetration was meaured by creating quantitative regions of interest around the outer and inner 50%-by-area images of the right lung after aerosol delivery. By convention, the left side was not analyzed because of possible confusion with stomach contents.[14] The outer edge of the images for each subject had been first defined as that of the equilibrium image of radioactive xenon gas, and hence represents the ventilated portion of the lung. We define penetration index (PI) as the ratio of γ-Cam counts in the outer area to counts in the inner area and, therefore, the higher the index the greater the penetration to the alveoli (Fig. 3). The PI is one method used to describe the penetration of

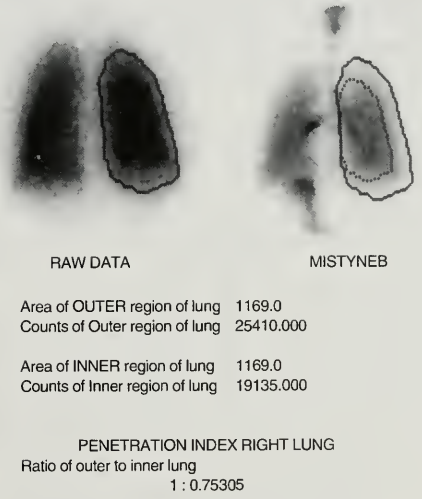
RAW DATA
MISTYNEB
Area of OUTER region of lung 1169.0
Counts of Outer region of lung 25410.000
Area of INNER region of lung 1169.0
Counts of Inner region of lung 19135.000
PENETRATION INDEX RIGHT LUNG
Ratio of outer to inner lung
1 : 0.75305

Fig. 3. Demonstration of inner and outer lung areas based on xenon lung scan.

aerosol into the lungs.[14] Another is the central-peripheral ratio, which is measured similarly but has the reverse connotation—that is, a deep penetration of aerosol into the lung results in a low central-peripheral ratio. For those investigators utilizing radioactive particles, the retained radioactivity at 24 hours is believed to represent deep penetration to the alveoli. A description of these techniques is found in the review by Agnew.[14]

Results

Particle-size testing revealed a mass median aerosol diameter (MMAD) of 0.51 μ for the C-system, whereas the M-neb produced a MMAD of 1.45 μ.

Composite data are provided in Table 1. Greater lung deposition (%Lung) occurred with the C-system. Extrapulmonary deposition (%GI) was reduced fivefold, and escape into the room (%Room) was reduced twofold. No difference was observed in either PI or %Dead.

Discussion

During the study, we made a number of observations. Some subjects of small stature with comparatively low breathing frequencies and tidal volumes seemed to be able to obtain virtually all of their inspiratory needs from the nebulizer output, and, therefore, the reservoir bag became distended and fixed. We did not alter flow to the nebulizer during the course of the study. However, we later found that reducing nebulizer flow optimized utility of the reservoir, but it was not clear whether this affected efficiency. (We did informal bench testing with radioactive aerosols, an inspiratory filter, and a mechanical 'lung' to optimize flowrate to nebulizer with minute ventilation of the lung, but because we do not know the effect on particle size, we cannot state that this improves efficiency in vivo.) Participation by the respiratory therapist, although not mandatory, was desirable to adjust the inspiratory resistor for best system operation. The reservoir bag can provide biofeedback if the subject is coached to watch the reservoir and take breaths of sufficient depth to deflate it.

Our data undoubtedly underestimate the amount of extrapulmonary deposition in the subjects participating in this study. In larger subjects, we were not able to encompass the entire pharyngeal-to-lower gastric area within view of the camera. We suspect that extrapulmonary deposition probably accounts for as much or more aerosol than is deposited in the lungs with a conventional nebulizer.

That we were unable to demonstrate a difference in penetration has two possible explanations. First, the finding could be valid in that the aerosol particles produced by small volume nebulizers may be thought of as two populations—larger particles unable to traverse dead space, baffles, and/or upper airways and smaller particles that enter the lung and penetrate to a variable degree depending on their size distribution. Alternatively, the finding may be an artifact of technique in that we do not correct for lung-volume depth beneath the planar surface observed by the camera. Hence deposition in the anteroposterior dimension is not assessed.

The Circulaire system appears to have advantages compared to conventional nebulization. The mean deposition efficiency is greater than that reported in studies of conventional nebulizers.[1-5] If we assume that the same doses of medication are to be administered, replacement of conventional nebulizers with the Circulaire should markedly reduce the side effects from sympathomimetic bronchodilators or steroids. Further, the Circulaire should reduce the risk to caregivers[15] and other

Table 1. Data from 10 Patients Using Conventional Nebulizer (M-Neb) and a New Nebulizer System (C-Sys)

	%Lungs*		%GI		%Room		Penetration Index		%Dead Volume	
Subject No.	M-Neb	C-Sys	M-Neb	C-Sys	M-Neb	C-Sys	M-Neb	C-Sys	M-Neb	C-Sys
1	8.0	11.2	3.5	1.3	34.8	11.8	0.50	0.38	36	36
2	9.1	19.8	4.2	1.2	37.3	19.7	0.43	0.36	28	25
3	9.0	17.4	2.4	1.1	26.7	7.4	0.33	0.48	54	42
4	8.1	5.7	6.5	0.3	41.3	33.9	0.42	0.46	25	37
5	6.5	10.2	3.6	1.1	34.3	7.0	0.59	0.37	41	36
6	12.3	8.7	4.6	0.6	29.1	21.0	0.41	0.59	38	35
7	7.3	9.6	13.2	1.8	27.6	16.0	0.59	0.59	33	39
8	8.0	19.7	5.1	1.1	22.9	0.8	0.40	0.38	46	51
9	8.7	13.3	7.6	1.6	29.5	5.2	0.34	0.58	34	42
Mean (SD)	8.6 (1.6)	12.8 (5.1)†	5.6 (3.3)	1.1 (0.5)†	31.5 (5.8)	13.9 (9.8)†	0.45 (0.10)	0.47 (0.10)	37 (9)	38 (7)

*%Lungs = % of aerosol deposited in the lungs; %GI = deposited in gastrointestinal tract; % room = deposited in environment (potentially); penetrtion index = ratio of radioactive particle count in outer region to count in the inner region of the lung; and %Dead Volume = % of radioactive solution remaining in the nebulizer.

†Statistically significant difference ($p < 0.05$).

patients associated with the venting of excess aerosol to the environment, although obviously any effective expiratory filter would serve the same function. With the biofeedback possible from the reservoir and the participation of the respiratory therapist, treatments may be more effective. A more intriguing possibility is that higher doses of medication might be utilized with a greater degree of safety. Although we have not directly tested the clinical benefit of high-dose bronchodilators, some evidence[16,17] suggests that true clinical benefit might be achieved for both bronchodilators and steroids.

PRODUCT SOURCES

Nebulizers:

Circulaire, WestMed Inc, Tucson AZ

Airlife Misty-Neb, Baxter HealthCare Corp, Pharmaseal Division, Valencia CA

Measuring Equipment & Supplies:

Model IPC-2AS Cascade Impactor, California Measurements Inc, Sierra Madre CA

Gamma camera, 400X C/T, GE Medical Systems, Milwaukee WI

Radioactive isotope, ^{99m}technetium diethylenetriamine-penta acetate (DPTA), Mallinckrodt Medical Inc, St Louis MO

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Predicting Aerosol Deposition during Neonatal Ventilation: Feasibility of Bench Testing

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STUDY QUESTION: Can in-vitro bench testing of neonatal pressure-controlled ventilators predict aerosol delivery to the lung? BACKGROUND: Lung deposition of an aerosolized drug is determined by the amount of drug inhaled (inhaled mass) and by the tendency of the lung to retain rather than exhale the aerosol. For adult aerosol delivery systems, in-vitro bench testing has resulted in increased lung deposition in clinical studies of spontaneously breathing and mechanically ventilated patients. However, it has been reported that bench testing of neonatal ventilator systems is not useful for predicting clinical deposition. PURPOSE OF THE STUDY: To assess whether perturbation of a bench model of neonatal ventilation in a manner likely to change aerosol delivery would result in proportional changes in deposition in an animal lung. METHODS: We measured aerosol delivery using a bench model of a pressure-controlled, continuous-flow, neonatal ventilator system delivering a typical range of minute ventilation (260-900 mL) to a test lung. A radioactive aerosol of ^{99m}Tc bound to human serum albumin was generated using a small-volume ultrasonic nebulizer and collected on a filter positioned distal to a 3.0-mm endotracheal tube (ETT) that determined inhaled mass. The nebulizer was placed at two locations: its conventional position in the inspiratory line (IL position) and just distal to the Y-piece of the ventilator (DY position) a position not clinically applicable but likely to increase aerosol delivery. After the bench studies, the two nebulizer-ventilator circuits and settings were used to deliver the radioaerosol to the lungs of mechanically ventilated rabbits and lung deposition was calculated using a gamma camera and attenuation-coefficient technique. RESULTS: Bench model, inhaled mass—using the DY configuration, 8.3 ± 0.94 % of the activity was delivered to the inhaled-mass filter compared to 1.6 ± 0.6 % in the IL configuration ($p < 0.0001$, DY:IL 5.2:1). Deposition in the ETT was similar in magnitude to the inhaled mass (DY vs IL configuration, 6.4 ± 1.7 % vs 1.4 ± 0.6 %, $p < 0.0001$) and correlated with the measured particle distributions. Rabbit model, lung deposition: DY configuration vs IL position 3.31 ± 2.1 % vs 0.56 ± 0.09 %, $p = 0.008$, DY:IL 5.9:1). CONCLUSIONS: Differences in aerosol delivery measured in an in-vitro bench model are found to be proportional to those detected in the lung. A significant quantity of nebulized particles deposit in the ETT. Therefore, bench testing may have a useful role in preliminary testing of aerosol delivery systems and nebulized drugs in the setting of neonatal ventilation. The clinical acceptance and safety of modifications to standard neonatal circuits (eg, dead-space effects and tubing modifications) require additional clinical studies. [Respir Care 1994;39(12):1162-1168.]

Dr O'Riordan and Dr Smaldone are associated with the Department of Medicine, Pulmonary/Critical Care Division; Dr Kleinman with the Department of Pediatrics, Division of Neonatal Medicine; and Mr Hughes with the Department of Respiratory Care—University Medical Center, State University of New York at Stony Brook, Stony Brook, New York.

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INTRODUCTION

In recent years, interest has been increasing in topical delivery of medications to the lung in the form of aerosols. The motivation for applying this mode of administration is the desire to maximize efficacy by concentrating drug in the target organ while limiting systemic toxicity. In order to measure the dose-response of an inhaled drug it is, of course, necessary to know the dose deposited in the patient's lungs. Unfortunately, the dose deposited in the lung cannot be extrapolated from the dose placed in the nebulizer, primarily because only a fraction

of the medication placed in the nebulizer is inhaled by the patient and the relative efficiency of commercially available nebulizer-ventilator delivery systems can vary by an order of magnitude.[1-4] To minimize this variability in adults, aerosol delivery systems have been tested on the bench before undertaking in-vivo clinical studies. In both spontaneously breathing patients[2,5] and adults on mechanical ventilation,[3,6] bench studies have predicted aerosol delivery to the lung.

Neonatal ventilator systems differ from adult systems in important ways. First, most are pressure controlled rather than volume controlled. Second, the minute volume, which is not measured in standard clinical practice, is usually between 250 and 750 mL/min compared to 5-20 L/min in the adult. Third, the diameter of the endotracheal tube (ETT) and other tubing used in the circuit is smaller and may prove to be a barrier to inhaled particles. Cameron et al[4] have demonstrated significant variability in the efficiency of commercially available nebulizers, in a bench model of pressure-controlled neonatal ventilation. Expressed as a percentage of the dose placed in the nebulizer, the amount of aerosol 'inhaled' by the test lung varied from 0.22 to 1.52 %. Rau and Harwood[7] using a bench setup similar to that of Cameron et al[4] demonstrated that modifying the ventilator circuit using a spacer, or holding chamber, in the inspiratory line increased aerosol delivery from 0.97 to 1.78% in one type of jet nebulizer. In contrast to the relatively inefficient aerosol delivery reported by Cameron et al[4] and Rau and Harwood,[7] Benson et al[8] using a different bench technique found that up to 12% of the dose of theophylline in a nebulizer could be delivered to a test lung. In none of these three studies was the predictive accuracy of the bench model tested by comparison to an animal or human model. Watterberg et al[9] tested the predictive ability of a bench model of a neonatal circuit in delivering cromoglycate to intubated neonates. Their bench protocol, which utilized two different experimental configurations, predicted markedly different lung deposition for each; but, when those configurations were tested in neonates, no differences in deposition were detected. However, the ventilator circuit in the bench model was not pressurized and did not precisely mimic the actual circuit used clinically. In a separate study, Flavin et al[10] used a rabbit model and found that 1-4% of the dose placed in the nebulizer was deposited in the rabbits' lungs, with the highest deposition being reported in animals treated with nebulizers producing submicronic particles. However, Flavin et al[10] used a volume-controlled ventilator; so, their study cannot be easily compared to that of Cameron et al,[4] Rau and Harwood,[7] Benson et al,[8] or Watterberg et al.[9]

If bench testing was to be shown to reliably assess factors that determine deposition in the lungs of neonates, then many of the technical issues related to the delivery of new drugs to neonates or the testing of new aerosol devices for neonates could be studied in advance of clinical patient studies. For example, choice of the most efficient commercial nebulizer or the need to modify ventilator tubing or ventilator settings could be assessed with preliminary bench experiments. In the present study, we used a bench model of a neonatal ventilator with typical ventilator settings, neonatal tidal volumes (V_Ts), and ETT and ventilator tubing, and captured the aerosol particles that would have been inhaled by a neonate (inhaled mass). We selected two modes of aerosol delivery that we believed (from preliminary testing) would likely result in different amounts' being 'inhaled' on the bench. Then, we compared the bench results with measured lung deposition in an animal preparation. If in-vitro bench predictions are accurate, differences between nebulizer configurations measured on the bench should be proportional to differences in lung deposition using the same nebulizer systems.

METHODS

Bench Protocol

A radiolabeled saline solution was nebulized and the aerosol delivered through a standard pressurized neonatal ventilator circuit to an absolute low-resistance filter placed at the distal end of an ETT. (For the purposes of this study, a low-resistance absolute filter is defined as a filter that captures all of the aerosol produced by a clinical nebulizer without significantly increasing resistance to gas flow.) The amount of radioactivity on this filter (measured in a well counter) defines the inhaled mass[1] and is expressed as a percentage of the radioactivity placed in the nebulizer (the nebulizer charge[1]). In our model, this measurement corresponds to the particles inhaled by a neonate ventilated using the same circuit and ventilator settings. The percentages of radioactivity depositing on the ETT, Y-piece, and on filters placed in the inhalation and exhalation tubing were also measured. Experiments were carried out with a range of minute volumes corresponding to the range of settings that might be encountered in a neonatal ICU and using 2 different positions for the nebulizer (breathing rate of 30 breaths/min with V_T of 8 mL and breathing rate of 60 breaths/min with V_T of 15 mL; peak inspiratory pressure was limited to 15 cm H_2O).

Ventilator Circuit

The ventilator circuit is illustrated in Figure 1. A pressure-controlled ventilator* was connected to a standard ventilator circuit in which the inspiratory and expiratory lines met at a Y-piece attached to an ETT (internal diameter 3.0 mm). Distal to the ETT was a cotton ball in a plastic holder (inhaled mass filter). A pneumotachograph was placed distal to

*Manufacturers and suppliers are identified in the Product Sources section at the end of the text.

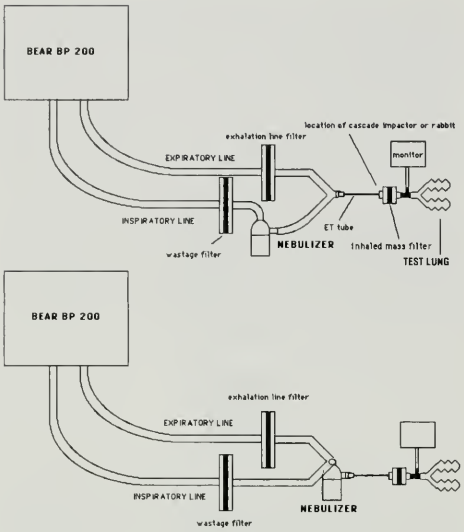

Fig. 1. A standard neonatal ventilator circuit is illustrated; *upper panel:* the ultrasonic nebulizer in the IL configuration (nebulizer 10 cm proximal to the Y-piece); *lower panel:* the DY configuration (nebulizer distal to the Y-piece).

the filter and attached to an electronic monitor, the NVM. The plastic test lungs were placed distal to the NVM. We used a commercially available test lung for 8-mL V_Ts, and customized a more compliant plastic lung in our laboratory to obtain a 15-mL V_T without significantly increasing peak airway pressure.

The 3.0-mm ETT was selected because this is the size most commonly used in our neonatal ICU. It was cut to a 10-cm length to conform with standard clinical practice in our NICU. For measurements of V_T during aerosol delivery, the monitoring device was placed distal to the absolute filter because if it had been placed proximal to the filter, particles might have deposited on the pneumotachograph. The V_T monitor was calibrated for accuracy using a pneumotachograph and integrator by passing a known volume through the device using a 30-mL syringe.

Filters

Low-resistance absolute filters were placed in the inspiratory and expiratory lines to capture any aerosol particles that may have been expelled through these lines. Particles theoretically could pass retrograde through the inspiratory line because of a safety feature of this ventilator that dissipates excess pressure in the circuit through this line. To avoid confusion with the inhaled-mass filter distal to the ETT (Fig. 1), the filter in the inspiratory line was designated as the upstream-wastage filter. The upstream-wastage filter and expiratory-line filters consisted of 17-cm diameter paper discs that fit snugly within a plastic container. Similar filters were used in our previous studies in adults.[5,7] However, these filters could not be used to sample the inhaled mass at the distal end of the ETT because the filter holder has a volume of 20 mL, a negligible volume in an adult ventilator circuit with a V_T of 500-1000 mL. However, in the neonate, V_Ts are often less than 10 mL, and particles inhaled into the 20-mL filter holder could be exhaled before depositing on the paper filter, thus underestimating the amount inhaled by the test lung. This problem was overcome by making smaller filters out of cotton balls with a smaller volume (< 1 mL). The resistance of the cotton ball to airflow was assessed by monitoring the V_T distal to the cotton-ball filter. It was noted that if the cotton ball became moistened the resistance to airflow increased significantly, as manifested by a reduction in V_T. To avoid this problem, the V_T was monitored throughout aerosol delivery and the cotton-ball filter was changed when the V_T decreased by more than 2 mL during the run. The filter's permeability to aerosol particles was tested by placing the cotton-ball filter and one of the low-resistance absolute filter papers in series and demonstrating that the cotton captured 99% of the radioactive particles that passed through the system.

Nebulizer and Circuit Location

A small-volume ultrasonic nebulizer was used rather than a jet nebulizer because the ultrasonic does not require additional gas flow to generate aerosol particles and, therefore, enabled us to experiment with changing the relationship between ventilator gas flow and the nebulizer baffling system. The nebulizer was placed at two different positions in the ventilator circuit. The first was in the inspiratory line 10 cm upstream from the Y-piece (Fig. 1), designated the inspiratory line (IL) configuration. In clinical practice, this is the conventional position for a nebulizer to be located. The nebulizer was also placed distal to the Y-piece with the ETT directly attached to the nebulizer (the DY configuration). This is not an approved location for an ultrasonic nebulizer because it could theoretically introduce significant dead space into the system and because there may be risks associated with attaching an ultrasonic nebulizer directly to the ETT. Extensive clinical testing would be required to establish its safety in clinical practice. Nevertheless, there are theoretical grounds for believing that aerosol delivery would be increased in this location, and the central purpose of our study was to establish whether a difference in aerosol deliv-

ery detectable with a bench model would also be detectable in an animal preparation.

The nebulizer was modified to run continuously rather than intermittently every 30 seconds. The one-way inspiratory valve on the nebulizer chamber was removed to facilitate attachment of the inspiratory line or Y-piece. To ensure an airtight seal with the ETT, a small plastic sleeve was interposed. The nebulizer was filled with 4 mL of 0.9% saline (the nebulizer charge[1]) labeled with technetium that was bound to human serum albumin (^{99m}Tc-HSA).

ETT and Y-Piece Deposition

After each bench study, the ETT was disconnected and placed in a plastic bag (to prevent loss of radioactive condensate) and radioactivity was measured in the well counter. Activity was also measured on the Y-piece and the tubing that connected it to the upstream-wastage and expiratory filters.

Particle Distribution

In order to measure aerodynamic particle distributions in a clinically relevant manner, the circuit shown in Figure 1 was modified. In a separate series of experiments, a cascade impactor was inserted into the circuit distal to the ETT but proximal to the inhalation filter and test lung. Sampling was performed for 1 minute with each configuration (cascade flow of 1.0 L/min).

Animal Protocol

The protocol was approved by the Animal Use Committee of the hospital. New Zealand White rabbits (weight 1.089 kg-2.25 kg) were anesthetized with ketamine and butyrophenone and paralyzed with pancuronium to prevent all spontaneous respiration, as part of a separate physiologic study. A tracheotomy was performed, and the airway was intubated with a 3.0-mm ETT, shortened to 10-cm. All of the animals died under this anesthetic regimen with death occurring as a result of circulatory failure. All but three of the experiments listed in Table 2 were performed after the animals had died but within 90 minutes of death. Lung-chest wall compliance may decrease with rigor mortis and thus V_T may decrease in a pressure-controlled system. This risk was minimized by limiting the time for completion of experiments to a maximum of 90 minutes post mortem and by checking V_T with an in-line neonatal V_T monitor immediately before each deposition run.

We performed 13 experiments on 6 rabbits, using the circuits illustrated in Figure 1. For each rabbit, using an anteriorly positioned gamma camera, serial images of aerosol deposition were obtained following aerosol inhalation from the DY and IL configurations. The images acquired by the camera were stored in a computer for later analysis. For each animal, the ETT was not removed for each deposition run and, consequently, ETT deposition was not measured via well counter. Further, the ETT orientation to the gamma camera was changed for the DY and IL experiments. This change in camera geometry precluded measurement of ETT deposition via the camera using the attenuation-coefficient technique. However, the rabbit was fixed in position, with respect to the camera, and lung deposition for each maneuver could be determined by serial subtraction of preceding images using regions of interest drawn around the lungs in a manner that excluded the ETT deposition. At the end of the experiment, for the purposes of calculating the attenuation coefficient of the chest wall and lungs, a final image of the lungs was obtained. Then, the lungs were surgically removed and counted in the well counter. This activity was decay corrected to the time of the last image, and an attenuation coefficient was calculated. Using the attenuation coefficient, lung counts from previous images could be converted to deposited radioactivity in millicuries.

RESULTS

The results of the bench model experiments are shown in Table 1. Using the DY configuration, inhaled mass delivered to the cotton-ball filter was 8.3 ± 0.94 % of the activity placed in the nebulizer compared to 1.6 ± 0.6 % when the nebulizer was placed in the IL configuration ($p < 0.0001$, unpaired t test). Aerosol delivery in the DY configuration ex-

Table 1. Bench Data for DY vs IL Configuration: Deposition of Radioacitivity Distal to ET Tube (Inhaled Mass) and in Exhalation-Line Filter

Configuration	Minute Ventilation (L)	Inhaled Mass (%)*	Exhalation Filter (%)
DY	0.26	9.30	29.00
DY	0.26	7.70	29.30
DY	0.90	8.80	30.50
DY	0.90	7.27	22.70
Mean ± SD		8.3 ± 0.94	27.88 ± 3.52
IL	0.87	1.90	17.60
IL	0.90	2.17	21.20
IL	0.54	2.10	27.80
IL	0.54	1.97	18.30
IL	0.24	0.77	30.60
IL	0.24	0.89	22.80
Mean ± SD		1.60 ± 0.6	23.05 ± 5.20
DY vs IL (t test)		p = 0.0001	p = 0.15
Ratio DY:IL		5.2:1	

*Percentages refer to % of initial quantity of radioactivity in nebulizer (nebulizer charge).

ceeded that of the IL configuration by a factor of 5.2:1. Significantly more aerosol particles were captured on the filter in the expiratory line than by the inhaled mass filter in both configurations (mean ± SD—IL configuration: % on expiratory filter 23.05 ± 5.20 %, $p < 0.0001$; DY configuration: 27.88 ± 3.51%, $p = 0.0001$, paired t test). With both configurations, a negligible quantity of particles was recovered from the filter placed in the inspiratory line (upstream-wastage filter). The time for the nebulizer to run to dryness was 10 minutes when placed in the IL configuration and 20 minutes in the DY configuration.

Deposition in the ETT was significantly greater in the DY configuration (DY vs IL configurations: 6.4 ± 1.7 % vs 1.4 ± 0.6 %, $p < 0.0001$, unpaired t test). In the Y-piece, deposition exceeded that of the ETT and there was no difference between configurations (DY vs IL: 19.7 ± 3.4 % vs 20.17 ± 6.9 %, $p = 0.92$, unpaired t test).

The mass median aerodynamic diameter (MMAD) ± geometric standard deviation (σ_g) for the particles sampled in the IL configuration was 1.41 ± 1.85 μ (n = 3); for the DY configuration the MMAD ± σ_g was 2.55 ± 1.8 μ (n = 2).

The results of the rabbit experiments are shown in Table 2. In the rabbits, particle deposition in the lungs was higher by a ratio of 5.9 to 1 with the DY configuration compared to the IL position (3.31 ± 2.1% vs 0.56 ± 0.09 %, $p = 0.008$, unpaired t test). As in the bench experiments, a significant amount of the nebulized particles was captured by the expiratory line filter, and they greatly exceeded lung deposition (mean ± SD IL configuration: % on expiratory filter = 27.43 ± 5.16 %, $p < 0.0001$, paired t test compared to lung; DY configuration: 32.47 ± 5.93 %, $p < 0.0001$).

Table 2. Rabbit Data for DY vs IL Configuration: Deposition in Lungs and Exhalation-Line Filter

Configuration	Minute Ventilation (L)	Kg	Lung Deposition (%)†	Exhalation Filter (%)
DY	0.72	2.16	1.40	21.2
DY	0.52	2.09	3.30	31.2
DY*	0.54	1.96	4.47	34.8
DY*	0.52	1.26	1.08	35.0
DY	0.44	1.09	1.49	29.2
DY	0.44	1.25	5.05	37.8
DY	0.44	1.25	6.39	38.1
Mean ± SD			3.3 ± 2.07	32.47 ± 5.93
IL	0.72	2.16	0.52	20.3
IL*	0.52	2.09	0.61	28.5
IL	0.54	1.96	0.39	24.7
IL	0.52	1.26	0.64	27.1
IL	0.44	1.09	0.61	36.0
IL	0.44	1.25	0.59	28.0
Mean ± SD			0.56 ± 0.09	27.43 ± 5.16
DY vs IL (t test)			$p = 0.008$	$p = 0.13$
Ratio DY IL			5.9:1	

* = alive

† Percentages refer to % of initial quantity of radioactivity in nebulizer (nebulizer charge).

DISCUSSION

The findings of the present study demonstrate that a bench model of neonatal ventilation is capable of detecting significant differences in the efficiency of aerosol delivery systems. Aerosol delivery in the DY configuration exceeded that of the IL configuration by a ratio of 5.2 to 1 in the bench model (expressed as the inhaled mass) and by a ratio of 5.9 to 1 in the animal model (expressed as lung deposition). Although the DY-IL ratios are similar for the bench and animal models, the inhaled mass measured on the bench regularly exceeded actual lung deposition in the rabbits. This latter finding is consistent with the experience from adult ventilator studies in which the inhaled-mass filter measures the amount inhaled (ie, there is no exhalation from an absolute filter), whereas the amount deposited in a lung is the net of the amount inhaled less the amount exhaled.[1] In ventilated and spontaneously breathing adult subjects, approximately 50%, on average, of the aerosol inhaled will be retained by the lung, the other half being exhaled.[5,6,11,12]

Previous studies of spontaneously breathing[5] and mechanically ventilated[6] adult patients have demonstrated that the choice and modification of aerosol delivery systems can affect the amount of aerosolized medication delivered to the lungs of these patients. Furthermore, it has been shown that prior bench testing of these delivery systems can be used to select the optimum method of aerosol delivery in these patient groups.[2,3] The findings of the present study suggest that the principles utilized in adults can be applied to bench models of neonatal ventilation. Appropriate in-vitro testing of neonatal delivery systems would facilitate the design of clinical trials of aerosolized medication by increasing the predictability of aerosol delivery.

The efficiency of delivery in the neonatal circuit is significantly less than that recently reported in adults (mean adult inhaled mass 30%[6]). The uniformly high quantities of captured particles found on the exhalation filter indicate that in an intact pressurized neonatal circuit significantly more aerosol passes directly into the exhaled line than enters the ETT. In the bench studies, because the inhaled-mass filter was an absolute low-resistance filter, no aerosol particles were exhaled by the test lung, hence those particles captured in the expiratory line represent aerosol that had passed directly into the expiratory line without being inhaled. With both configurations, a negligible quantity of particles was recovered from the filter placed in the inspiratory line (upstream-

wastage filter) indicating that with an ultrasonic nebulizer retrograde flow of aerosol does not occur to an important degree.

The aerosol wastage in the expiratory line can be attributed to the flow patterns of neonatal ventilator systems (ie, gas at 6-10 L/min typically passes through a neonatal ventilator). Because the average neonate has a minute ventilation of 250-500 mL, most of the ventilator gas flow (and, consequently, the aerosol carried by the gas) never enters the neonate and instead passes directly out the expiratory line. This may help to explain the findings of Watterberg et al[9] who used a bench model of ventilator tubing but not a complete pressurized neonatal circuit (ie, complete circuit with a ventilating test lung). For example, in their bench model of neonatal ventilator circuitry, they found that using a conventional jet nebulizer charged with 2 mL of cromolyn, 20.5% the dose placed in the nebulizer was recovered leaving the nebulizer, whereas only 5.5% was recoverable after passage through 60 cm of ventilator tubing and an ETT adapter. Hence, their bench model identified factors (choice of nebulizer and placement in ventilator tubing) that seemed to affect aerosol delivery to an important degree. However in a follow-up clinical study on intubated, ventilated babies that used urinary excretion of cromolyn as an index of lung deposition, it was found that < 1% of the dose placed in the nebulizer was deposited in the lungs regardless of choice of nebulizer or its position in the ventilator circuit. The absence of a pressurized ventilator circuit simulating the clinical situation in the model of Watterberg et al is the most likely explanation as to why the bench findings were not replicated in their in-vivo experiments.

In the bench model of the present study, V_T was monitored by an in-line pneumotachograph. In contrast to adult volume-controlled ventilators, most pressure-controlled neonatal ventilators do not measure V_T. Failure to verify the V_T in a bench model may explain the results of the study by Benson et al,[8] which reported unusually high deposition of aerosolized theophylline (12% of the nebulizer charge) collected in a saline bag by dissolution. They modified a standard pressurized neonatal circuit by introducing a needle into the collection bag to prevent accumulation of "excess volume." This leak distal to the ETT may not have been large enough to produce a detectable change in the pressure of the ventilator circuit, but it may have significantly increased the minute volume, and this may account for the unusually high delivery of aerosol they reported.

In addition to simulating the pattern of gas flow typical of a clinical situation, the bench model needs to include an appropriately sized ETT. In adults, ETT and connectors can be important sites of deposition, but usually represent about one third of the total quantity of particles deposited in a patient.[6] In the present study, ETT and Y-piece deposition equaled and exceeded, respectively, the inhaled mass. ETT deposition appeared related to particle distribution. That is, for the DY configuration, with the larger particle distribution, both inhaled mass and ETT deposition significantly exceeded that of the IL configuration.

We can only speculate as to the mechanisms underlying the differences in time of nebulization and efficiency in the two configurations. They are most likely due to an interaction between the baffling system of the nebulizer and the differences in flow pattern between the two configurations. In the IL configuration, 10 L/min of air enter at the top of the nebulizer cap and exit through the side port of the nebulizer cap from whence the aerosol proceeds to the Y-piece. In the DY configuration, 10 L/min of air enter through the Y-piece now on the top of the nebulizer and only 0.5 L leaves the side port and enters the ETT. The remaining 9.5 L exit through the Y-piece at top of the nebulizer (Fig. 1). Thus, it is likely that more air flushes the nebulizer in the IL configuration, shortening the time to dryness. The particles leaving the ETT were also larger in the DY configuration consistent with the greater ETT deposition. This factor may also contribute to the greater inhaled mass.

The purpose of this study was to test the feasibility of bench testing neonatal ventilator systems. Although we did find increased delivery on the bench and in the lungs for the DY configuration, we are not able to recommend at this stage that ultrasonic nebulizers can be safely placed distal to the Y-piece in clinical practice. It is theoretically possible that sufficient mixing of exhaled gas with 'fresh' gas from the ventilator may occur to prevent problems with increased dead space, but clinical testing is required to confirm this suggestion. Any variation in nebulizer design should be formally tested for its effects on dead space if the nebulizer is to be placed distal to the Y-piece.

CONCLUSIONS

In neonatal ventilation, differences in aerosol delivery measured in an in-vitro bench model are found to be proportional to those detected in animals. Therefore, bench testing may have a useful role in preliminary testing of aerosol delivery systems and nebulized drugs in the setting of neonatal ventilation, provided that certain conditions are met. First, an intact pressurized circuit ventilating a test lung is necessary because the flow characteristics of the intact ventilator circuit are important determinants of nebulizer performance during neonatal ventilation. Second, the model must incorporate an appropriate ETT and Y-piece connector identical to those which will be used in the clinical study, as these are significant sites of deposition. Third, the compliance of test lungs should be tested by placement of a V_T monitor in-line and ensuring that appropriate neonatal ventilator settings will produce appropriate neonatal V_Ts.

ACKNOWLEDGMENTS

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PRODUCT SOURCES

Nebulizer:
Aerosonic, DeVilbiss Health Care, Somerset PA

Ventilator:
BP 200, Bear Medical Systems, Riverside CA

Gamma Camera:
Picker Dyna Camera 4, Northford CT

Computer:
Advanced Medical Computer, Sunnyvale CA

Electronic Monitor:
NVM, Bear Medical Systems, Riverside CA

Plastic Surrogate Lung:
Bear Medical Systems, Riverside CA

Pneumotachograph:
Fleisch #1, Switzerland

Integrator and Recorder:
Grass Model P7, Grass Instruments, Quincy MA

Filter Paper:
Paper 5305, Hollingsworth and Vose, West Groton PA

Cotton Balls:
Johnson & Johnson Consumer Products, Del Rio TX

Cascade Impactor:
GS1, California Measurements, Sierra Madre CA

Radioisotope Calibrator:
CRC-10R, Capintec, Montvale NJ

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The American Association for Respiratory Care Clinical Practice Guidelines

- **Metabolic Measurement Using Indirect Calorimetry during Mechanical Ventilation**
- **Transcutaneous Blood Gas Monitoring for Neonatal and Pediatric Patients**
- **Capillary Blood Gas Sampling for Neonatal and Pediatric Patients**
- **Body Plethysmography**

Respir Care 1994;39(12):1170-1190

Previously Published Guidelines:

- Ventilator Circuit Changes
- Delivery of Aerosols to the Upper Airway
- Neonatal Time-Triggered, Pressure-Limited, Time Cycled Mechanical Ventilation
- Application of Continuous Positive Airway Pressure to Neonates via Nasal Prongs or Nasopharyngeal Tube
- Surfactant Replacement Therapy
- Static Lung Volumes

Respir Care 1994;39(8):797-836

- Transport of the Mechanically Ventilated Patient
- Fiberoptic Bronchoscopy Assisting
- Resuscitation in Acute Care Hospitals
- Intermittent Positive Pressure Breathing
- Bland Aerosol Administration

Respir Care 1993;38(11):1169-1200

- Directed Cough
- Endotracheal Suctioning of Mechanically Ventilated Adults and Children with Artificial Airways
- In-Vitro pH and Blood Gas Analysis and Hemoximetry
- Single-Breath Carbon Monoxide Diffusing Capacity
- Use of Positive Airway Pressure Adjuncts to Bronchial Hygiene Therapy

Respir Care 1993;38(5):495-521

- Patient-Ventilator System Checks
- Humidification during Mechanical Ventilation
- Selection of Aerosol Delivery Device
- Nasotracheal Suctioning
- Bronchial Provocation
- Exercise Testing for Evaluation of Hypoxemia and/or Desaturation
- Arterial Blood Gas Sampling
- Oxygen Therapy in the Home or Extended Care Facility

Respir Care 1992;37(8):855,856,882-922

- Incentive Spirometry
- Pulse Oximetry
- Oxygen Therapy in the Acute Care Hospital
- Spirometry
- Postural Drainage Therapy

Respir Care 1991;36(12):1398-1426

AARC Clinical Practice Guideline

Metabolic Measurement using Indirect Calorimetry during Mechanical Ventilation

MMMV 1.0 PROCEDURE:

Metabolic measurements using indirect calorimetry for determination of oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), and resting energy expenditure (REE) as an aid to patient nutritional assessment and management;[1-5] assessment of weaning success and outcome;[6-8] and assessment of the relationship between O_2 delivery ($\dot{D}_{O_2}$) and $\dot{V}_{O_2}$[1,9,10]—this guideline addresses metabolic measurement during mechanical ventilation.

MMMV 2.0 DESCRIPTION/DEFINITION:

Metabolic measurements use an indirect calorimeter to measure $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ via expired gas analysis. The measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are used to calculate RQ ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) and REE using the Weir equation:[11]

$$REE = [\dot{V}_{O_2}(3.941) + \dot{V}_{CO_2}(1.11)]\ 1440\ \text{min/day}.$$

The measurement of REE in mechanically ventilated patients has been shown to be more accurate than published formulas used to predict REE,[12-26] to reduce the incidence of overfeeding and underfeeding,[12-26] and to decrease costs associated with total parenteral nutrition (TPN).[26] Measurement of REE and RQ has been shown to be helpful in designing nutritional regimens to reduce $\dot{V}_{CO_2}$ in patients with chronic obstructive pulmonary disease (COPD) and patients requiring mechanical ventilation.[13,27-32] Despite this evidence, studies demonstrating improved outcome, improved weaning success, or shorter ICU/hospital stay are lacking.

The objectives of metabolic measurements by indirect calorimetry are

2.1 To accurately determine the REE of mechanically ventilated patients to guide appropriate nutritional support;[12-26]
2.2 To accurately determine RQ to allow nutritional regimens to be tailored to patient needs;[12-32]
2.3 To accurately determine REE and RQ to monitor the adequacy and appropriateness of current nutritional support;[12-32]
2.4 To allow determination of substrate utilization when urinary nitrogen values are concomitantly measured;[33-35]
2.5 To determine the O_2 cost of breathing as a guide to the selection of ventilator mode, settings, and weaning strategies;[6-8]
2.6 To monitor the $\dot{V}_{O_2}$ as a guide to targeting adequate $\dot{D}_{O_2}$.[1]

MMMV 3.0 SETTING:

3.1 Mechanically ventilated patients
- **3.1.1** In the hospital
- **3.1.2** In the extended care facility

MMMV 4.0 INDICATIONS:

Metabolic measurements may be indicated

4.1 In patients with known nutritional deficits or derangements.[36] Multiple nutritional risk and stress factors that may considerably skew prediction by Harris-Benedict equation include
- **4.1.1** neurologic trauma,[18-25]
- **4.1.2** paralysis,[25]
- **4.1.3** COPD,[13,21,24,32]
- **4.1.4** acute pancreatitis,[16]
- **4.1.5** cancer with residual tumor burden,[14]
- **4.1.6** multiple trauma,[20,23,26]
- **4.1.7** amputations,[23]
- **4.1.8** patients in whom height and weight cannot be accurately obtained.[36]

4.1.9 patients who fail to respond adequately to estimated nutritional needs,[19]
4.1.10 new patients on home TPN,[36]
4.1.11 patients who are unable to eat and who require mechanical ventilation for > 5 days,[36]
4.1.12 transplant patients,[36]
4.1.13 morbidly obese patients,[36]
4.1.14 severely hypermetabolic or hypometabolic patients.

4.2 When the desire or perceived need is present to measure the O_2 cost of breathing in mechanically ventilated patients.[6-8]
4.3 When the need exists to assess the $\dot{V}_{O_2}$ in order to evaluate the hemodynamic support of mechanically ventilated patients.[1,9,10]

MMMV 5.0 CONTRAINDICATIONS:

When a specific indication is present, there are no contraindications to performing a metabolic measurement using indirect calorimetry unless short-term disconnection of ventilatory support for connection of measurement lines results in hypoxemia, bradycardia, or other adverse effects.[37,38]

MMMV 6.0 HAZARDS/COMPLICATIONS:

Performing metabolic measurements using an indirect calorimeter is a safe, noninvasive procedure with few hazards or complications. Under certain circumstances and with particular equipment the following hazards/complications may be seen.

6.1 Closed circuit calorimeters may cause a reduction in alveolar ventilation due to increased compressible volume of the breathing circuit.[5,39-41]
6.2 Closed circuit calorimeters may decrease the trigger sensitivity of the ventilator and result in increased patient work of breathing.[5,39-41]
6.3 Short-term disconnection of the patient from the ventilator for connection of the indirect calorimetry apparatus may result in hypoxemia, bradycardia, and patient discomfort.[37,38]
6.4 Inappropriate calibration or system setup may result in erroneous results causing incorrect patient management.[1,4,5]

MMMV 7.0 LIMITATIONS OF PROCEDURE:

Limitations of the procedure include

7.1 Accurate assessment of REE and RQ may not be possible[42-44] because of patient condition or certain bedside procedures or activities.
7.2 Inaccurate measurement of REE and RQ may be caused by leaks of gas from the patient/ventilator system preventing collection of expired gases including:
7.2.1 leaks in the ventilator circuit,[1,4,5]
7.2.2 leaks around tracheal tube cuffs or uncuffed tubes,[1,4,5]
7.2.3 leaks through chest tubes or bronchopleural fistula.[45]
7.3 Inaccurate measurement of REE and RQ occurs during peritoneal and hemodialysis due to removal across the membrane of CO_2 that is not measured by the indirect calorimeter.[1,4,5,15]
7.4 Inaccurate measurement of REE and RQ during open circuit measurement may be caused by
7.4.1 instability of delivered oxygen concentration (F_{DO_2}) within a breath or breath to breath due to changes in source gas pressure and ventilator blender/mixing characteristics;[46,47]
7.4.2 $F_{DO_2} > 0.60$;[1,4,5,46,47]
7.4.3 inability to separate inspired and expired gases due to bias flow from flow-triggering systems, IMV systems, or specific ventilator characteristics;[1,4,5,48,49]
7.4.4 the presence of anesthetic gases or gases other than O_2, CO_2, and nitrogen in the ventilation system;[47]
7.4.5 the presence of water vapor resulting in sensor malfunction;
7.4.6 inappropriate calibration;[50]
7.4.7 connection of the indirect calorimeter to certain ventilators, with adverse effect on triggering mechanism, increased expiratory resistance, pressure measurement, or maintenance of the ventilator.[5]
7.4.8 total circuit flow exceeding internal gas flow of indirect calorimeter that incorporates the dilutional principle.[51]
7.5 Inaccurate measurement of REE and RQ

during closed circuit measurement may be caused by

7.5.1 short duration of the measurement period (a function of CO_2 absorber life and $\dot{V}_{CO_2}$) that may not allow REE state to be achieved;[5,39-41]

7.5.2 changes in functional residual capacity (FRC) resulting in changes in spirometer volume unassociated with $\dot{V}_{O_2}$;[5,39-41]

7.5.3 leaks drawing gas into the system during spontaneous breathing measurements that adds volume to the system and cause erroneously low $\dot{V}_{O_2}$ readings;[5,39-41]

7.5.4 increased compressible volume in the circuit that prevents adequate tidal volume delivery resulting in alveolar hypoventilation and changes in $\dot{V}_{CO_2}/\dot{V}_{O_2}$;[5,39-41]

7.5.5 increased compressible volume and resistance that results in difficulty triggering the ventilator and increased work of breathing.[5,39-41]

MMMV 8.0 ASSESSMENT OF NEED:

Metabolic measurements should be performed only on the order of a physician after review of indications (MMMV 4.0) and objectives.

MMMV 9.0 ASSESSMENT OF TEST QUALITY AND OUTCOME:

9.1 Test quality can be evaluated by determining whether

9.1.1 RQ is consistent with the patient's nutritional intake;[1-5]

9.1.2 RQ rests in the normal physiologic range (0.67 to 1.3);[1-5]

9.1.3 measured $\dot{V}_{O_2}$ is within ±10% of the mean value and measured $\dot{V}_{CO_2}$ within ±6% of the mean value;[5]

9.1.4 REE has been defined as the value obtained with the patient lying in bed, awake and aware of his/her surroundings.[42] (This state should have been observed for 10-15 minutes associated with results in 9.1.3.)

9.2 Outcome may be assessed by the interpretation and confirmation/manipulation of patient nutritional support regimen by a physician or nutritionist based on the measurement results.

9.3 Outcome may be assessed by the successful manipulation of the mechanical ventilator settings and/or hemodynamic management based on the measurement of the $\dot{V}_{O_2}$.

MMMV 10.0 RESOURCES:

10.1 Indirect calorimeter, open- or closed-circuit design.

10.1.1 The calibration gas mixture should be relevant to the concentration of gas to be measured clinically.[1-5]

10.1.2 The indirect calorimeter should be calibrated on the day of measurement and more often if errors in measurement are suspected.[1-5]

10.1.3 When the measurement results are suspect and/or when repeated calibration attempts are marked by instability, the indirect calorimeter may be tested via an independent test method (burning ethanol or other substance with a known RQ or adding known flows of CO_2 and nitrogen to simulate $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$).[52-55] As a simple test, ventilation of a leak-free system should yield $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ values of near 0. Routinely scheduled measurement of normal control subjects (volunteers) may be useful.

10.2 A method of stabilizing F_{DO_2} during open-circuit measurements should be available and may include

10.2.1 an air-oxygen blender connected between the gas source and the ventilator inlets for high pressure gas;[46]

10.2.2 an inspiratory mixing chamber between the ventilator main flow circuit and the humidifier.[56]

10.3 An isolation valve, double-piloted exhalation valve, or other device to separate inspiratory and expiratory flow should be incorporated when using continuous flow in the ventilator circuit.[48]

10.4 Personnel: Due to the level of technical and patient assessment skills required, metabolic measurements using indirect calorimeters should be performed by individuals trained in and with the demonstrated and documented ability to

10.4.1 calibrate, operate, and maintain an

indirect calorimeter;

10.4.2 operate a mechanical ventilator, including knowledge of the air-oxygen blending system, the spontaneous breathing mechanisms, and the alarm and monitoring functions;

10.4.3 recognize metabolic measurement values within the normal physiologic range and evaluate the results in light of the patient's current nutritional and clinical status;

10.4.4 assess patient hemodynamic and ventilatory status and make recommendations on appropriate corrective/therapeutic maneuvers to improve or reverse the patient's clinical course.

A relevant credential (eg, RRT, CRTT, RN, or RPFT) is desirable.

MMMV 11.0 MONITORING:

11.1 The following should be evaluated during the performance of a metabolic measurement to ascertain the validity of the results:

11.1.1 clinical observation of the resting state (MMMV 9.1.4);

11.1.2 patient comfort and movement during testing;

11.1.3 values in concert with the clinical situation;

11.1.4 equipment function;

11.1.5 results within the specifications listed in 9.1.3.

11.2 Measurement data should include a statement of test quality and list the current nutritional support, ventilator settings, and vital signs.

MMMV 12.0 FREQUENCY:

12.1 Metabolic measurements should be repeated according to the clinical status of the patient and indications for performing the test. The literature suggests that more frequent measurement may be necessary in patients with a rapidly changing clinical course as recognized by

12.1.1 hemodynamic instability,[42]

12.1.2 spiking fevers.[42]

12.2 Patients in the immediate postoperative period and those being weaned from mechanical ventilation may also need more frequent measurement.[42]

MMMV 13.0 INFECTION CONTROL:

Metabolic measurements using indirect calorimetry are relatively safe procedures, but a remote possibility of cross-contamination exists either via patient-patient or patient-caregiver interface. The following guidelines should be followed when a metabolic measurement is performed.

13.1 Universal Precautions should be exercised whenever equipment (isolation valves) is contaminated with blood or other body fluids.[57]

13.2 Appropriate use of barriers and handwashing is recommended.

13.3 Tubing used to direct expiratory gas from the ventilator to the indirect calorimeter should be disposed of or cleaned between patients.

13.4 Connections used in the inspiratory limb of the circuit proximal to the humidifier should be wiped clean between patients; equipment distal to the humidifier should be disposed of or subjected to high-level disinfection between patients.

13.5 Bacteria filters may be used to protect equipment in both the inspired and expired lines, but caution should be used that moisture does not increase filter resistance resulting in poor gas sampling flow or increased resistance to exhalation.

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AARC Clinical Practice Guideline

Transcutaneous Blood Gas Monitoring for Neonatal & Pediatric Patients

TCM 1.0 PROCEDURE:

Transcutaneous monitoring of oxygen (P_{tcO_2}) and carbon dioxide (P_{tcCO_2}) in neonates, infants, and small children—this guideline does not address the application of transcutaneous monitoring in adults and older children.

TCM 2.0 DESCRIPTION/DEFINITION:

Transcutaneous monitoring measures skin-surface P_{O_2} and P_{CO_2} to provide estimates of arterial partial pressure of oxygen and carbon dioxide (P_{aO_2} and P_{aCO_2}). The devices induce hyperperfusion by local heating of the skin and measure the partial pressure of oxygen and carbon dioxide electrochemically.[1,7]

TCM 3.0 SETTING:

Transcutaneous monitoring may be performed by trained personnel in a variety of settings including (but not limited to) hospitals, extended care facilities, and patient transport.[8]

TCM 4.0 INDICATIONS:

4.1 The need to monitor the adequacy of arterial oxygenation and/or ventilation[9,10]

4.2 The need to quantitate the response to diagnostic and therapeutic interventions as evidenced by P_{tcO_2} and/or P_{tcCO_2} values[9-11]

TCM 5.0 CONTRAINDICATIONS:

In patients with poor skin integrity and/or adhesive allergy, transcutaneous monitoring may be relatively contraindicated.[9]

TCM 6.0 HAZARDS/COMPLICATIONS:

P_{tcO_2} and/or P_{tcCO_2} monitoring is considered a safe procedure, but because of device limitations, false-negative and false-positive results may lead to inappropriate treatment of the patient.[10,12,13] In addition, tissue injury may occur at the measuring site (eg, erythema, blisters, burns, skin tears).[1,8,10]

TCM 7.0 DEVICE LIMITATIONS/VALIDATION OF RESULTS:

P_{tcO_2} is an indirect measurement of P_{aO_2} and, like P_{aO_2}, does not reflect oxygen delivery or oxygen content. Complete assessment of oxygen delivery requires knowledge of hemoglobin, saturation, and cardiac output. In a similar way, P_{tcCO_2} is an indirect measurement of P_{aCO_2} but knowledge of delivery and content is not necessary to use P_{tcCO_2} as an indicator of adequacy of ventilation.

7.1 Factors, agents, or situations that may affect readings, limit precision, or limit the performance or application of a transcutaneous monitor include

7.1.1 Technical:

7.1.1.1 The procedure may be labor intensive, although newer designs make application quicker and simpler.[14]

7.1.1.2 Prolonged stabilization time is required following electrode placement.[14,15]

7.1.1.3 Manufacturers state that electrodes must be heated to produce valid results; however, clinical studies suggest that valid results may be obtained with P_{tcCO_2} electrodes operated at lower than recommended temperatures or with no heat.[16]

7.1.1.4 The theoretical basis for mandatory heating of the P_{tcO_2} electrode is established.[2]

7.1.1.5 Improper calibration is possible and may be difficult to detect.[17]

7.1.2 Clinical: The following factors may increase the discrepancy between arterial and transcutaneous values—

7.1.2.1 The presence of hyperoxemia

(P_{aO_2} > 100 torr),[12,13]

7.1.2.2 The presence of a hypoperfused state (shock, acidosis),[8,18,19]

7.1.2.3 Improper electrode placement or application,[8]

7.1.2.4 Vasoactive drugs,[19]

7.1.2.5 The nature of the patient's skin and subcutaneous tissue (skinfold thickness, edema).[8,20]

7.2 Validation: Arterial blood gas values should be compared to transcutaneous readings taken at the time of arterial sampling in order to validate the transcutaneous values. This validation should be performed initially and periodically as dictated by the patient's clinical state.[8,17]

7.2.1 During validation studies in patients with functional shunts, electrode site and arterial sampling site should be on the same side of the shunt.[10,21]

7.2.2 When disparity exists between transcutaneous and arterial values and the clinical presentation of the patient, possible causes should be explored before results are reported. Discrepancies may be reduced by monitoring at alternate sites, recalibration, or appropriate substitution of instruments. If such steps do not remedy the disparity, transcutaneous results should not be reported; instead a statement describing the corrective action should be included in the patient's chart and some other mode of monitoring should be established (eg, pulse oximetry and/or arterial blood analysis). The absolute limits that constitute unacceptable disparity vary with patient condition and specific device. Clinical judgment must be exercised.

7.3 To help assure consistency of care based on transcutaneous blood gas readings, the operator should verify that

7.3.1 High- and low-limit alarms are set appropriately;

7.3.2 Appropriate electrode temperature is set;

7.3.3 Electrode placement is appropriate and systematic electrode-site change occurs;

7.3.4 Specific manufacturer's recommendations for maintenance, operation, and safety are complied with.

TCM 8.0 ASSESSMENT OF NEED:

8.1 When direct measurement of arterial blood is not available or accessible in a timely fashion, P_{tcO_2} and/or P_{tcCO_2} measurements may temporarily suffice if the limitations of the data are appreciated.[9]

8.2. Transcutaneous blood gas monitoring is appropriate for continuous and prolonged monitoring (eg, during mechanical ventilation, CPAP, and supplemental oxygen administration).[9,10]

8.3 P_{tcO_2} values can be used for diagnostic purposes as in the assessment of functional shunts (eg, persistent pulmonary hypertension of the newborn, PPHN, or persistent fetal circulation[21-23]) or to determine the response to oxygen challenge in the assessment of congenital heart disease.[21-23]

TCM 9.0 ASSESSMENT OF OUTCOME:

9.1 Results should reflect the patient's clinical condition (ie, validate the basis for ordering the monitoring).[3,5,7]

9.2 Documentation of results, therapeutic intervention (or lack of), and/or clinical decisions based on the transcutaneous measurements should be noted in the medical record.

TCM 10.0 RESOURCES:

10.1 Equipment: Transcutaneous monitor, electrodes, calibration gases, and associated expendable supplies—the monitor should have been validated by the manufacturer, using appropriate quality control procedures and clinical reliability studies.

10.2 Personnel: Licensed or credentialed respiratory care practitioners or other credentialed persons with equivalent training and demonstrated ability to exercise the necessary clinical judgment, assess the patient, and perform the essential tasks of calibration and application[8]

TCM 11.0 MONITORING:

The monitoring schedule of patient and equipment during transcutaneous monitoring should be integrated into patient assessment and vital signs determinations. Results should be documented in the patient's medical record and should detail the condi-

tions under which the readings were obtained:

11.1 The date and time of measurement, transcutaneous reading, patient's position, respiratory rate, and activity level;
11.2 Inspired oxygen concentration or supplemental oxygen flow, specifying the type of oxygen delivery device;
11.3 Mode of ventilatory support, ventilator, or CPAP settings;
11.4 Electrode placement site, electrode temperature, and time of placement;
11.5 Results of simultaneously obtained P_{aO_2}, P_{aCO_2}, and pH when available;
11.6 Clinical appearance of patient, subjective assessment of perfusion, pallor, and skin temperature.

TCM 12.0 FREQUENCY:

Transcutaneous blood gas monitoring should be continuous for development of trending data. So-called spot checks are not appropriate.[3,9,10]

TCM 13.0 INFECTION CONTROL:

No special precautions are necessary, but Universal Precautions (as described by the Centers for Disease Control) are recommended.[24,25]

13.1 The device probe should be cleaned between patient applications according to manufacturer recommendations.
13.2 The external portion of the monitor should be cleaned according to manufacturer's recommendations whenever the device remains in a patient's room for prolonged periods, when soiled, or when it has come in contact with potentially transmissible organisms.

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AARC Clinical Practice Guideline

Capillary Blood Gas Sampling for Neonatal & Pediatric Patients

CBGS 1.0 PROCEDURE:

Capillary sampling for blood gas analysis

CBGS 2.0 DESCRIPTION:

Capillary blood gas (CBG) samples may be used in place of samples from arterial punctures or indwelling arterial catheters to estimate acid-base balance (pH) and adequacy of ventilation (P_{aCO_2}).[1-3] Capillary P_{O_2} measurements are of little value in estimating arterial oxygenation.[4-6]

A puncture or small incision is made with a lancet or similar device into the cutaneous layer of the skin at a highly vascularized area (heel, finger, toe). (The lancet may be used freehand or as part of a device that limits puncture depth.) To accelerate blood flow and reduce the difference between the arterial and venous gas pressures, the area is warmed prior to the puncture. As the blood flows freely from the puncture site, the sample is collected in a heparinized glass capillary tube.[7-9]

CBGS 3.0 SETTING:

Capillary sampling may be performed by trained health care personnel in

3.1 Acute care hospitals,
3.2 Clinics,
3.3 Physician offices,
3.4 Extended care facilities,
3.5 Homes.

CBGS 4.0 INDICATIONS:

Capillary blood gas sampling is indicated when

4.1 Arterial blood gas analysis is indicated but arterial access is not available.
4.2 Noninvasive monitor readings are abnormal: transcutaneous values, end-tidal CO_2, pulse oximetry.
4.3 Assessment of initiation, administration, or change in therapeutic modalities (ie, mechanical ventilation) is indicated.
4.4 A change in patient status is detected by history or physical assessment.
4.5 Monitoring the severity and progression of a documented disease process is desirable.

CBGS 5.0 CONTRAINDICATIONS:

5.1 Capillary punctures should not be performed
5.1.1 at or through the following sites:[10]
5.1.1.1 posterior curvature of the heel, as the device may puncture the bone;[11]
5.1.1.2 the heel of a patient who has begun walking and has callus development;[12]
5.1.1.3 the fingers of neonates (to avoid nerve damage);[13]
5.1.1.4 previous puncture sites;[14,15]
5.1.1.5 inflamed, swollen, or edematous tissues;[14,15]
5.1.1.6 cyanotic or poorly perfused tissues;[14,15]
5.1.1.7 localized areas of infection;[14,15]
5.1.1.8 peripheral arteries.
5.1.2 on patients less than 24 hours old, due to poor peripheral perfusion;[1]
5.1.3 when there is need for direct analysis of oxygenation;[1-3]
5.1.4 when there is need for direct analysis of arterial blood;
5.2 Relative contraindications include
5.2.1 peripheral vasoconstriction;[1]
5.2.2 polycythemia (due to shorter clotting times);[1]

5.2.3 hypotension may be a relative contraindication.[1]

CBGS 6.0 HAZARDS/COMPLICATIONS:

6.1 Infection
- **6.1.1** Introduction of contagion at sampling site and consequent infection in patient, including calcaneus osteomyelitis[9,16] and cellulitis
- **6.1.2** Inadvertent puncture or incision and consequent infection in sampler

6.2 Burns
6.3 Hematoma
6.4 Bone calcification[14]
6.5 Nerve damage[9]
6.6 Bruising
6.7 Scarring[12]
6.8 Puncture of posterior medial aspect of heel may result in tibial artery laceration[11]
6.9 Pain
6.10 Bleeding
6.11 Inappropriate patient management may result from reliance on capillary P_{O_2} values.[17,18]

CBGS 7.0 LIMITATIONS OF METHOD/ VALIDATION OF RESULTS:

7.1 Limitations
- **7.1.1** Inadequate warming of the site prior to a puncture may result in capillary values that correlate poorly with arterial pH and P_{CO_2} values.[19,20]
- **7.1.2** Undue squeezing of the puncture site may result in venous and lymphatic contamination of the sample.[14]
- **7.1.3** A second puncture may be needed to obtain an adequate amount of blood for analysis.
- **7.1.4** Variability in capillary P_{O_2} values precludes using these samples for assessing oxygenation status.[1,2,3,18,20,21]

7.2 Validation of results
- **7.2.1** Sample must be anticoagulated and obtained anaerobically with capillary tube filled completely and air bubbles expelled immediately. Sample should be immediately chilled or analyzed within 10-15 minutes if left at room temperature.[22]
- **7.2.2** A respiratory assessment of the patient should be documented in the medical record at the time a capillary sample is performed (See 11.0 Monitoring).
- **7.2.3** An arterial sample may be analyzed to compare with the capillary pH and P_{CO_2} values.

CBGS 8.0 ASSESSMENT OF NEED:

Capillary blood gas sampling is an intermittent procedure and should be performed when a documented need exists. Routine or standing orders for capillary puncture are not recommended. The following may assist the clinician in assessing the need for capillary blood gas sampling:

8.1 History and physical assessment;[23]
8.2 Noninvasive respiratory monitoring values
- **8.2.1** Pulse oximetry;[23]
- **8.2.2** Transcutaneous values;
- **8.2.3** End-tidal CO_2 values;

8.3 Patient response to initiation, administration, or change in therapeutic modalities;[23-25]
8.4 Lack of arterial access for blood gas sampling.[1-3]

CBGS 9.0 ASSESSMENT OF TEST QUALITY:

Sampling of capillary blood is useful for patient management only if the procedure is carried out according to an established quality assurance program. The validity of the test may be jeopardized if any of the following occur:[10,26,27]

9.1 The sample is contaminated by air;
9.2 Clots prevent accurate analysis;
9.3 Quantity of sample is insufficient for analysis;
9.4 Analysis of sample is delayed (> 15 minutes for samples at room temperature, or > 60 minutes for samples held at 4°C).[22]

CBGS 10.0 RESOURCES:

10.1 Equipment: Single puncture—preheparinized glass capillary (eg, Natelson) tubes, metal fleas, magnet, clay/wax sealant or caps,

lancet to make incision < 2.5 mm in depth, gauze/cotton balls, ice, gloves, skin antiseptic, warm and moist cloth/diaper or commercially prepared warming pads (42°C), sharps container, labeling materials[10]

10.2 Personnel: Capillary sampling must be performed under direction of a physician. Individuals who perform capillary sampling should have a background in mathematics and science and specific training in capillary blood sampling and related procedures. They must competently demonstrate capillary blood gas sampling and undergo periodic skills assessment of technique: implementation of Universal Precautions; success at obtaining a quality sample; preparation, storage and transport of specimens; documentation; and post sampling site care and/or complication rate.[10,28,29]

CBGS 11.0 MONITORING:

The following should be monitored and documented in the medical record as part of the capillary sampling procedure:

11.1 F_{IO_2} or prescribed oxygen flow;[10,23,28,29]
11.2 Oxygen administration device or ventilator settings;[10,23,27,28]
11.3 Free flow of blood without the necessity for 'milking' the foot or finger to obtain a sample;[10,14]
11.4 Presence/absence of air or clot in sample;[10,26,27]
11.5 Patient temperature, respiratory rate, position or level of activity, and clinical appearance;[10,27]
11.6 Ease or difficulty of obtaining sample;[10,27,28]
11.7 Appearance of puncture site;[14,15]
11.8 Complications or adverse reactions to the procedure;
11.9 Date, time, and sampling site;[10]
11.10 Noninvasive monitoring values: transcutaneous O_2 & CO_2, end-tidal CO_2, and/or pulse oximetry;[23]
11.11 Results of the blood gas analysis.

CBGS 12.0 FREQUENCY:

The frequency of capillary sampling should depend upon the clinical status of the patient and the indications for performing the procedure, not upon a prescribed frequency.

12.1 Those patients requiring frequent CBGs should be considered candidates for placement of an indwelling arterial access for blood gas sampling or noninvasive monitoring techniques, to limit trauma associated with repeated punctures.

12.2 Repeated puncture of the foot/finger increases the risk of scarring or serious laceration. Care should be exercised to alternate the sampling site for patients requiring multiple punctures.[14,15]

CBGS 13.0 INFECTION CONTROL:

13.1 Universal Precautions as published by the Centers for Disease Control and directives issued by the Department of Labor concerning occupational exposure to blood-borne pathogens must be followed during capillary sampling.[29,30]

13.2 Aseptic techniques should be employed due to the invasive nature of this procedure. Puncture site should be cleaned with antiseptic solution.[10]

13.3 Blood specimens, contaminated materials, and lancets must be disposed of in appropriate containers.[29]

13.4 Gloves should be worn by caregivers to protect against blood splashes on sores or skin breaks.[29]

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Body Plethysmography

BP 1.0 PROCEDURE:

Body plethysmography for thoracic gas volume and airways resistance measurements

BP 2.0 DESCRIPTION/DEFINITION:

During body plethysmography, the subject is enclosed in a chamber equipped to measure pressure, flow, or volume changes. The most common measurements made using the body plethysmograph are thoracic gas volume (V_{TG}) and airways resistance (R_{aw}).[1,2] Airways conductance (G_{aw}) is also commonly calculated as the reciprocal of R_{aw}. Specific airways conductance (ie, conductance/unit of lung volume) is routinely reported as SG_{aw}. Other tests that can be measured in the body plethysmograph include spirometry, bronchial challenge, diffusing capacity (D_{LCO}), single-breath nitrogen (N_2), multiple-breath N_2 washout, pulmonary compliance, occlusion pressure, and cardiac output, including pulmonary blood flow. These will not be discussed as part of this guideline because some have been previously addressed.[3-6]

2.1 V_{TG} is expressed in liters (BTPS) and is the volume of gas in the lung when the mouth shutter is closed. In plethysmographic studies, it is commonly used to represent the functional residual capacity (FRC).
2.2 Airways resistance (R_{aw}) is reported in cm H_2O/L/s.
2.3 Specific airways conductance (SG_{aw}) is reported in L/s/cm H_2O (ie, cm $H_2O \cdot s \cdot L^{-1}$) and is the reciprocal of the R_{aw} ($1/R_{aw}$) divided by the lung volume at which the resistance measurement was made.

BP 3.0 SETTINGS:

3.1 Pulmonary function laboratories
3.2 Cardiopulmonary laboratories
3.3 Clinics and physician's offices

BP 4.0 INDICATIONS:

Body plethysmographic determination of V_{TG}, R_{aw}, and SG_{aw} may be indicated

4.1 For measurement of lung volumes to distinguish between restrictive and obstructive processes;
4.2 For evaluation of obstructive lung diseases, such as bullous emphysema and cystic fibrosis, which may produce artifactually low results if measured by helium dilution or N_2 washout[7] (an index of trapped gas (ie, $FRC_{plethysmograph}/FRC_{He\ dilution}$) can be established);[8]
4.3 For measurement of lung volumes when multiple repeated trials are required, or when the subject is unable to perform multibreath tests;[9]
4.4 For evaluation of resistance to airflow;[10]
4.5 For determination of the response to bronchodilators (R_{aw}, SG_{aw}, and V_{TG});[11]
4.6 For determination of bronchial hyperreactivity in response to methacholine, histamine, or isocapnic hyperventilation (V_{TG}, R_{aw}, and SG_{aw});[12,13]
4.7 For following the course of disease and response to treatment.

BP 5.0 CONTRAINDICATIONS:

Relative contraindications to body plethysmography are

5.1 Mental confusion, muscular incoordination, body casts, or other conditions that prevent the subject from entering the plethysmograph cabinet or adequately performing the required maneuvers (ie, panting against a closed shutter);
5.2 Claustrophobia that may be aggravated by entering the plethysmograph cabinet;

as continuous I.V. infusions with pumps or other equipment that will not fit into the plethysmograph, that should not be discontinued, or that might interfere with pressure changes (eg, chest tube, transtracheal O_2 catheter, or ruptured eardrum);

5.4 continuous oxygen therapy that should not be temporarily discontinued.

BP 6.0 HAZARDS/COMPLICATIONS:

6.1 V_{TG} and R_{aw} measurements require the subject to pant against a closed shutter; improper panting technique may result in excessive intrathoracic pressures.

6.2 Enclosure in the plethysmograph may cause symptoms of claustrophobia.

6.3 Prolonged confinement in the plethysmograph chamber could result in hypercapnia or hypoxia; however, because of the limited length of the test and the fact that the plethysmograph must be vented periodically, this is an uncommon occurrence.

6.4 Transmission of infection is possible via improperly cleaned equipment (ie, mouthpieces) or as a consequence of the inadvertent spread of droplet nuclei or body fluids (patient-to-patient or patient-to-technologist).

BP 7.0 LIMITATIONS OF METHODOLOGY/ VALIDATION OF RESULTS:

Limitations of the body plethysmograph in measurement of V_{TG}, R_{aw}, and SG_{aw} include but are not limited to

7.1 Overestimation of V_{TG} in subjects with moderate or severe obstruction.[14,15]

7.2 Erroneous measurement of V_{TG}, R_{aw}, or SG_{aw} due to improper panting technique. Excessive pressure fluctuations or signal drift during panting may invalidate V_{TG}, R_{aw}, or SG_{aw}.[17]

7.3 Nonpanting measurements have been suggested for use in children or others who have difficulty mastering the panting maneuver.[18,19] Nonpanting maneuvers in plethysmographs with built in thermal leaks may invalidate V_{TG} or R_{aw} measurements.[2,20]

7.4 Computer-determined slopes of either V_{TG} or R_{aw} tangents may be inaccurate. Many systems calculate the slopes using a best-fit regression analysis. This technique may produce widely varying results if extraneous data points are included (due to improper panting or excessive signal drift).[21,22]

7.5 Excessive abdominal gas or panting techniques using accessory muscles may increase the measured V_{TG}, due to compression effects.[23]

7.6 Plethysmography is a complex test. Careful calibration of multiple transducers is required. Attention to frequency response, thermal stability, and leaks is necessary.[24]

7.7 Choice and application of reference values affect interpretation.

7.7.1 Reference values for V_{TG} using plethysmographically determined lung volumes are not widely available.

7.7.1.1 Make a tentative selection from whatever published reference values are available. The characteristics of the healthy reference population should match the study group with respect to age, body size, gender, and racial and ethnic mix. The equipment, techniques, and measurement conditions should be similar.

7.7.1.2 Following selection of apparently appropriate reference values, compare measurements obtained from a representative sample of healthy individuals (10-20 subjects) over an appropriate age range to the predicted values obtained from the selected reference values. If an appreciable number of the sample fall outside of the normal range, more appropriate reference values should be sought. This procedure detects only relatively gross differences between sample and reference populations.[25]

BP 8.0 ASSESSMENT OF NEED:

See Section 4.0 Indications.

BP 9.0 ASSESSMENT OF TEST QUALITY:

Each laboratory should standardize procedures and demonstrate intertechnician reliability. Test results can only be considered valid if they are derived according to and conform to established laboratory control and quality assurance protocols. These protocols should address test standardization and reproducibility criteria that include the methodology used to derive and report V_{TG} and airway mechanics.

9.1 Results are valid if the equipment functions acceptably and the subject is able to perform the maneuvers in an acceptable and reproducible fashion.

9.1.1 V_{TG} maneuvers may be considered acceptable when

9.1.1.1 the displayed or recorded tracing indicates proper panting technique; the P_{mouth}/P_{box} loop (closed shutter) should be closed or nearly so. The patient should support his/her cheeks with the hands to prevent pressure changes induced by the mouth.[26] This should be done without supporting the elbows or elevating the shoulders.

9.1.1.2 Recorded pressure changes should be within the calibrated pressure range of each transducer (See Section 10.1.3). The entire tracing should be visible. Pressure changes that are too large or too small may yield erroneous results.

9.1.1.3 There should be evidence of thermal equilibrium; tracings should not drift on the display or recording.

9.1.1.4 The panting frequency should be approximately 1 Hz. Nonpanting maneuvers may be acceptable if the plethysmograph system is specifically designed to perform such a maneuver.[14,27]

9.1.2 The reported V_{TG}

9.1.2.1 should be averaged from a minimum of 3-5 separate, acceptable panting maneuvers;[28,29]

9.1.2.2 should be calculated using tangents or angles that agree within 10% of the mean; widely varying tangents or angles should be averaged, and reported as variable;

9.1.2.3 should indicate whether the thoracic volume was at FRC or at another level;

9.1.2.4 should be compared with other lung volume determinations (He dilution, N_2 washout) if performed;

9.1.2.5 from some systems should be corrected for patient weight.

9.1.3 A slow vital capacity (VC) maneuver and its subdivisions inspiratory capacity (IC) and expiratory reserve volume (ERV) should be performed during the same testing session. The ERV, IC, and IVC can be measured before disconnecting the patient from the measuring system. Alternatively, the patient can be disconnected and the ERC, IC, and IVC performed imediately afterward.

9.1.3.1 The largest VC obtained should be used for calculation of derived lung volumes (ie, total lung capacity, or TLC, residual volume, or RV, and RV/TLC%).

9.1.3.2 The IC and ERV from the largest acceptable VC should be used to calculate derived volumes.

9.1.3.3 TLC may be calculated from the FRC determined plethysmographically:

$$TLC = FRC + IC$$

or

$$TLC = RV + VC.$$

9.1.3.4 RV may be calculated from the FRC determined plethysmographically:

$$RV = FRC - ERV$$

or

$$RV = TLC - VC.$$

9.1.4 R_{aw} and SG_{aw} maneuvers may be considered acceptable if they meet criteria 9.1.1.2 through 9.1.1.4 above.

9.1.4.1 The open shutter panting maneuver should show a relatively

closed loop, particularly in the range of +0.5 to –0.5 L/s.

9.1.4.2 The panting frequency during serial measurements in a given patient should be kept the same to aid in interpretation. Consensus of the group suggests a range of 1.5-3.0 Hz.

9.1.5 The reported R_{aw} and SG_{aw}

9.1.5.1 should be calculated from the ratio of closed and open shutter tangents for each maneuver.[30] Airway resistance and lung volume are interdependent in a nonlinear fashion;

9.1.5.2 should be averaged from 3-5 separate, acceptable maneuvers as calculated in 9.1.5.1; reproducibility should be within 10%;[31]

9.1.5.3 should have the open-shutter tangent (V/P_{box}) measured between flows of +0.5 and –0.5 L/s. For loops that display hysteresis, the inspiratory limbs may be used;[30]

9.1.5.4 Should have the SG_{aw} calculated using the V_{TG} at which the shutter was closed for each individual maneuver.[23]

9.2 Report of test results should contain a statement, by the technician performing the test, about test quality and if, appropriate which recommendations were not met.[32-34]

BP 10.0 RESOURCES:

10.1 Equipment:

10.1.1 Volume-measuring devices used in the plethysmograph (pneumotachometer) should meet or exceed ATS recommendations. A 3-L syringe should be available for calibration.[33]

10.1.2 Either pressure (constant volume) or flow-type plethysmographs may be used.

10.1.3 Transducers in the plethysmograph should meet the following range specifications:[23]

Mouth pressure: ±20 to 50 cm H_2O
Box pressure: ±2 cm H_2O (500 L box)
Flow: 0.2 to 1.5 L/s

10.1.4 Pressure and volumes signals should be phase aligned up to 10 Hz.

10.1.5 A plenum or similar device that facilitates thermal equilibrium is recommended. Some plethysmographs utilize air conditioning to maintain thermal equilibrium.

10.1.6 The plethysmograph cabinet should be easy for the subject to enter and exit. The door should preferably be operable from within the box. The cabinet should be equipped with an intercom and should provide adequate visibility for both the technologist and the subject.

10.1.7 The plethysmograph system, if computerized, should allow for technologist adjustment of open- and closed-shutter tangents.

10.1.8 Calibration devices should include (in addition to a 3-L syringe) 30-50 mL sine-wave pump (variable speed, used primarily for calibration of pressure boxes), water manometer ±20 cm H_2O (used for calibration of the mouth pressure transducer), and rotameter 0 to 1.5 L/s (used for calibration of the pneumotachometer).

10.1.9 An isothermal lung analog[35] and/or biologic controls[34] are recommended for quality control.

10.2 Personnel: Plethysmography should be performed under the direction of a physician trained in pulmonary function testing. It may be performed by persons who meet criteria for either Level I or Level II. Plethysmographic results can be compromised if the test is performed by inadequately trained personnel.

10.2.1 Level I: The technologist performing plethysmography should be a high school graduate or equivalent with a demonstrated ability to perform spirometry and lung volume determinations. Level I personnel should perform plethysmography only under the supervision of a Level II individual or a physician.

10.2.2 Level II: Personnel supervising plethysmography should have formal education and training.[36] This may be part of an accredited program in respiratory therapy or pulmonary function technology, or 2 years of college work in biological sci-

ences and mathematics. Level II personnel should also have 2 or more years experience performing spirometry, lung volumes, and diffusing capacity tests. One or more of the following credentials is recommended: CRTT, RRT, CPFT, RPFT, RN.

BP. 11.0 MONITORING:

(See also Section 9.0 Assessment of Test Quality)

11.1 The final report should contain a statement regarding test quality.
11.2 The final report should contain the V_{TG}, R_{aw}, and SG_{aw}, if performed. If the V_{TG} is measured at a lung volume other than FRC, both values should be reported.
11.3 If the FRC is measured by more than one method, the report should indicate how lung volumes are reported.

BP 12.0 FREQUENCY:

The frequency with which plethysmography is repeated should depend on the clinical question(s) to be answered.

BP 13.0 INFECTION CONTROL:

Plethysmographic tests are relatively safe procedures, but the possibility of cross-contamination exists, either from the patient-patient or patient-technologist interface.

13.1 Universal Precautions[37,38] (as published by the Centers for Disease Control) should be applied in all instances in which there is evidence of contamination with blood (eg, mouthpieces). Although Universal Precautions do not apply to saliva or mucus unless it contains blood, it should be noted that other potentially hazardous organisms may be present in these fluids even in the absence of blood, and the appropriate use of barriers and hand washing is recommended.[39]
13.2 Due to the nature of the maneuvers and the likelihood of coughing when the test is performed by subjects with known or suspected active infection with *M tuberculosis* or other airborne organisms, the following precautions are recommended.

13.2.1 The room in which the test is performed should meet or exceed the recommendations of U.S. Public Health Service[40] for air changes and ventilation. Ideally, an area in the testing department should be specially ventilated for isolation patients. If this is not possible, the patient should be returned to the isolation room as soon as possible.
13.2.2 Pulmonary function technologists performing procedures on patients with potentially infectious airborne diseases should wear a personal respirator that meets OSHA recommendations, especially if the testing itself induces cough.

13.3 The mouthpiece and any parts of the system that come into contact with the subject should be disposable or sterilized between patients. If sterilization is not feasible, then high-level disinfection should be performed. It is unnecessary to routinely clean the plethysmograph itself.
13.4 Bacteria filters may be used in circuits that allow rebreathing, although their efficacy is not well documented. Such filters may impose added resistance and increase the volume of the measuring device. If a filter is used in the plethysmograph, its resistance and volume should be subtracted from the R_{aw} and V_{TG}, respectively.

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Guideline for Prevention of Nosocomial Pneumonia

CENTERS FOR DISEASE CONTROL AND PREVENTION

Hospital Infection Control Practices Advisory Committee Members, February 1994

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PART I. ISSUES ON PREVENTION OF NOSOCOMIAL PNEUMONIA, 1994

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INTRODUCTION

This 2-part document updates and replaces the previously published Centers for Disease Control and Prevention Guideline for Prevention of Nosocomial Pneumonia (*Infect Control* 1982;3: 327-33, *Respir Care* 1983;28:221-32, and *Am J Infect Control* 1983;11:230-44). The revised guideline is designed to reduce the incidence of nosocomial pneumonia and intended for use by personnel who are responsible for surveillance and control of infections in acute-care hospitals. The guideline may not be applicable in long-term care facilities because of the unique characteristics of these settings.

The revised guideline addresses common problems encountered by infection control practitioners regarding the prevention and control of nosocomial pneumonia in U.S. hospitals. Sections on the prevention of bacterial pneumonia in mechanically ventilated and/or critically ill patients, care of respiratory-therapy devices, prevention of cross-contamination, and prevention of viral lower respiratory tract infections, such as respiratory syncytial virus (RSV) and influenza infections, have been expanded and updated. New sections on Legionnaires' disease and pneumonia due to *Aspergillus* spp. have been added. Lower respiratory tract infection due to *Mycobacterium tuberculosis* is not addressed in this document; it is covered in separate guidelines.[1]

A working draft of the guideline has been reviewed by experts in infection control, pulmonology, respiratory therapy, anesthesiology, internal medicine, and pediatrics. However, all recommendations in the guideline may not reflect the opinions of all reviewers.

Part I, "Issues on Prevention of Nosocomial Pneumonia—1994," provides the background for the consensus recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC) in Part II, "Recommendations for Prevention of Nosocomial Pneumonia." HICPAC was established in 1991 to provide advice and guidance to the Secretary and the Assistant Secretary for Health, Department of Health and Human Services; the Director, CDC; and the Director, NCID, CDC, regarding the practice of hospital infection control and strategies for surveillance, prevention, and control of nosocomial infections in U.S. hospitals. The committee also advises the CDC on periodic updating of guidelines and other policy statements regarding prevention of nosocomial infections. The Guideline for Prevention of Nosocomial Pneumonia is the first of a series of CDC guidelines being revised by HICPAC and NCID, CDC.

Part I can be an important resource for educating health-care workers regarding prevention and control of nosocomial respiratory tract infections. Because education of health-care workers is the cornerstone of an effective infection control program, hospitals should give high priority to continuing infection control educational programs for these staff members.

SUMMARY

Pneumonia is the second most common nosocomial infection in the United States and is associated with substantial morbidity and mortality. Most patients with nosocomial pneumonia are those with extremes of age, severe underlying disease, immunosuppression, depressed sensorium, and cardiopulmonary disease, and those who have had thoracoabdominal surgery. Although patients with mechanically assisted ventilation do not comprise a major proportion of patients with nosocomial pneumonia, they have the highest risk of developing the infection.

Most bacterial nosocomial pneumonias occur by aspiration of bacteria colonizing the oropharynx or upper gastrointestinal tract of the patient. Intubation and mechanical ventilation greatly increase the risk of nosocomial bacterial pneumonia because they alter first-line patient defenses. Pneumonias due to *Legionella* spp., *Aspergillus* spp., and influenza virus are often caused by inhalation of contaminated aerosols. Respiratory syncytial virus (RSV) infection usually follows viral inoculation of

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the conjunctivae or nasal mucosa by contaminated hands.

Traditional preventive measures for nosocomial pneumonia include decreasing aspiration by the patient, preventing cross-contamination or colonization via hands of personnel, appropriate disinfection or sterilization of respiratory therapy devices, use of available vaccines to protect against particular infections, and education of hospital staff and patients. New measures under investigation involve reducing oropharyngeal and gastric colonization by pathogenic microorganisms.

BACTERIAL PNEUMONIA

I. Etiologic Agents

The reported distribution of etiologic agents causing nosocomial pneumonia varies between hospitals because of differences in patient populations and diagnostic methods employed.[2-10] In general, however, bacteria have been the most frequently isolated pathogens.[2-6,9,11-13] Schaberg et al reported that in 1986-1989, aerobic bacteria comprised at least 73%, and fungi 4%, of isolates from sputum and tracheal aspirates from pneumonia patients at the University of Michigan Hospitals and hospitals participating in the National Nosocomial Infection Surveillance System (NNIS); very few anaerobic bacteria and no viruses were reported, probably because anaerobic and viral cultures were not performed routinely in the reporting hospitals (Table 1).[3] Similarly, cultures of bronchoscopic specimens from mechanically ventilated patients with pneumonia have rarely yielded anaerobes.[5-7,9,11,14,15] Only the report by Bartlett, which was based mainly on cultures of transtracheal aspirates from patients not receiving mechanically assisted ventilation, showed a predominance of anaerobes.[4]

Nosocomial bacterial pneumonias are frequently polymicrobial,[4,7,9,11,12,15-19] and gram-negative bacilli are the usual predominant organisms (Table 1).[2-6,9,11-13] However, *Staphylococcus aureus* (especially methicillin-resistant *S aureus*)[5,7,10,15,20,21] and other gram-positive cocci, including *Streptococcus pneumoniae*,[5,7] have recently emerged as significant isolates.[14] In addition, *Haemophilus influenzae* has been isolated from mechanically ventilated patients with pneumonia that occurs within 48-96 hours after intubation.[3,5,12,15,22] In NNIS hospitals, *Pseudomonas aeruginosa*, *Enterobacter* sp., *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, and *Proteus* spp. comprised 50% of the isolates from cultures of respiratory tract specimens from patients for whom nosocomial pneumonia was diagnosed by using clinical criteria; *S aureus* accounted for 16%, and *H influenzae*, for 6% (Table 1).[3] Fagon and co-workers reported that gram-negative bacilli were present in 75% of quantitative cultures of protected-specimen brushings (PSB) from patients who had received mechanically assisted ventilation and acquired nosocomial pneumonia; 40% of the cultures were polymicrobial.[5] In the report by Torres et al, 20% of pathogens recovered from cultures of PSB, blood, pleural fluid, or percutaneous lung aspirate were gram-negative bacilli in pure culture, and 17% were polymicrobial; however, 54% of specimens did not yield any microorganism, probably because of receipt of antibiotics by patients.[5]

II. Diagnosis

Nosocomial pneumonia has been difficult to diagnose.[7,8,16,23-32] Frequently, the criteria for diagnosis have been fever, cough, and development of purulent sputum, in combination with radiologic evidence of a new or progressive pulmonary infiltrate, a suggestive Gram's stain, and cultures of sputum, tracheal aspirate, pleural fluid, or blood.[3,4,23,25,33-36] Although clinical criteria together with cultures of sputum or tracheal specimens may be sensitive for bacterial pathogens, they are highly nonspecific, especially in patients with mechanically assisted ventilation;[8,9,12-15,18,24-26,29,31,37-42] on the other hand, cultures of blood or pleural fluid have very low sensitivity.[8,18,19,43]

Because of these problems, a group of investigators recently formulated consensus recommendations for standardization of methods to diagnose pneumonia in clinical research studies of ventilator-associated pneumonia.[44-46] These methods involve bronchoscopic techniques, eg, quantitative culture of PSB,[5,7-9,13,15,27,31,38,41,47,48] bronchoalveolar lavage (BAL),[7,12,41,47,49-54] and protected BAL (pBAL).[14] The reported sensitivities and specificities of these methods have ranged from 70% to 100% and 60% to 100%, respectively, depending on the tests or diagnostic criteria they were compared with. Because these techniques are invasive, they may cause complications such as hypoxemia, bleeding, or arrhythmia.[8,13,42,44,52,55,56] In addition, the sensitivity of the PSB procedure may decrease for patients receiving antibiotic therapy.[9,13,27] Nonbronchoscopic (NB) procedures, eg, NB-pBAL[12,27,57,58] or NB-PSB,[13] which utilize blind catheterization of the distal airways, and quantitative culture of endotracheal aspirate,[59,60] have been developed recently. Of these, endotracheal aspirate culture appears to be the most practical. The use of these bronchoscopic and nonbronchoscopic diagnostic tests can be a major step in better defining the epidemiology of nosocomial pneumonia especially in patients with mechanically assisted ventilation; however, further studies are needed to determine each test's applicability in daily clinical practice.

III. Epidemiology

NNIS reports that pneumonias (diagnosed on the basis of the CDC surveillance definition of nosocomial pneumonia) account for approximately 15% of all hospital-associated infections and are the second most common nosocomial infections after those of the urinary tract.[2,61] In 1984, the overall incidence of lower respiratory tract infection was 6 per 1,000 discharged patients.[2] The incidence per 1,000 discharged patients ranged from 4.2 in nonteaching hospitals to 7.7 in university-affiliated hospitals, probably reflecting institutional differences in the level of patients' risk for acquiring nosocomial pneumonia.

Nosocomial bacterial pneumonia often has been identified as a postoperative infection.[62,63] In the Study of the Efficacy of Nosocomial Infection Control in the 1970s, 75% of reported cases of nosocomial bacterial pneumonia occurred in patients who had had a surgical operation; the risk was 38 times greater for thoracoabdominal procedures than for those involving other body sites.[63] More recent epidemiologic studies, including NNIS studies, have identified other subsets of patients at high risk of developing nosocomial bacterial pneumonia: patients with endotracheal intubation and/or mechanically assisted ventilation, depressed level of consciousness (particularly those with closed-head injury), prior episode of a large-volume aspiration, or underlying chronic lung disease, and patients > 70 years of age. Other risk factors include 24-hour ventilator-circuit changes, fall-winter sea-

Table 1. Microorganisms Isolated from Respiratory Tract Specimens Obtained by Various Representative Methods from Adult Patients with a Diagnosis of Nosocomial Pneumonia

	Schaberg[3]	Bartlett[4]	Fagon[5]	Torres[6]
Hospital Type	NNIS & UMH*	Veterans	General	General
Patients Studied:				
Ventilated or nonventilated	Mixed	Mixed	Ventilated	Ventilated
Number	N/A†	159	49	78
Number of Episodes of Pneumonia	N/A	159	52	78
Specimen(s) Cultured	Sputum, tracheal aspirate	Transtracheal aspirate, pleural fluid, blood	Protected specimen brushing	Protected specimen brushing, lung aspirate, pleural fluid, blood
Culture Results:				
No organism isolated	N/A	0	0	54%‡
Polymicrobial	N/A	54%‡	40%‡	13%‡
Number of isolates	15,499	314	111	N/A
Aerobic Bacteria				
Gram-Negative Bacilli	50%**	46%††	75%††	16%‡‡
Pseudomonas aeruginosa	17%**	9%††	31%††	5%‡‡
Enterobacter sp.	11	4	2	0
Klebsiella sp.	7	23	4	0
Escherichia coli	6	14	8	0
Serratia sp.	5	0	0	1
Proteus sp.	3	11	15	1
Citrobacter sp.	1	0	2	0
Acinetobacter calcoaceticus	N/A	0	15	9
Others	N/A	0	10	0
Haemophilus influenzae	6%**	17%††	10%††	0%‡‡
Legionella sp.	N/A	N/A	2%††	2%‡‡
Gram-Positive Cocci	17%**	56%††	52%††	4%‡‡
Staphylococcus aureus	16%**	25%††	33%††	2%‡‡
Streptococcus sp.	1	31	21	2
Others	0	0	8	0
Anaerobes	N/A	35%††	2%††	0
Peptostreptococcus	N/A	14%††	N/A	0
Fusobacterium sp.	N/A	10	N/A	0
Peptococcus sp.	N/A	11	N/A	0
Bacteroides melaninogenicus	N/A	9	N/A	0
Bacteroides fragilis	N/A	8	N/A	0
Fungi	4% *	N/A	0	1%‡‡
Aspergillus sp.	N/A	N/A	0	1%‡‡
Candida sp.	4%**	N/A	0	0
Viruses	N/A	N/A	N/A	N/A

*NNIS & UMH = National Nosocomial Infections Surveillance System and University of Michigan Hospitals.
†N/A = Not applicable: not tested or not reported.
‡Percent episodes.
**Percent isolates.
†† Percent episodes (percentages not additive due to polymicrobial etiology in some episodes).
‡‡ Percent patients with pure culture.
References appear at the end of the document.

son, stress-bleeding prophylaxis with cimetidine with or without antacid, administration of antimicrobials, presence of a nasogastric tube, severe trauma, and recent bronchoscopy.[6,34,35,64-74]

Recently, NNIS stratified the incidence density of nosocomial pneumonia by patients' use of mechanical ventilator and type of intensive care unit (ICU). From 1986 to 1990, the median rate of ventilator-associated pneumonia per 1,000 ventilator-days ranged from 4.7 in pediatric ICUs to 34.4 in burn ICUs.[66] In contrast, the median rate of nonventilator-associated pneumonia per 1,000 ICU-days ranged from 0 in pediatric and respiratory ICUs to 3.2 in trauma ICUs.

Nosocomial pneumonia has been associated with high fatality rates. Crude mortality rates of 20%-50% and attributable mortality rates of 30%-33% have been reported; in one study, pneumonia comprised 60% of all deaths due to nosocomial infections.[17,35,74-80] Patients receiving mechanically assisted ventilation have higher mortality rates than do patients not receiving ventilation support; however, other factors, such as a patient's underlying disease(s) and organ failure, are stronger predictors of death in patients with pneumonia.[34,74]

Analyses of pneumonia-associated morbidity have shown that pneumonia could prolong hospitalization by 4-9 days.[79-83] A conservative estimate of the direct cost of excess hospital stay due to pneumonia is $1.2 billion a year for the nation.[83] Because of its reported frequency, associated high fatality rate, and attendant costs, nosocomial pneumonia is a major infection control problem.

IV. Pathogenesis

Bacteria may invade the lower respiratory tract by aspiration of oropharyngeal organisms, inhalation of aerosols containing bacteria, or, less frequently, by hematogenous spread from a distant body site (Figure 1). In addition, bacterial translocation from the gastrointestinal tract has been recently hypothesized as a mechanism for infection. Of these routes, aspiration is believed to be the most important for both nosocomial and community-acquired pneumonia.

In radioisotope-tracer studies, 45% of healthy adults were found to aspirate during sleep.[84] Persons with abnormal swallowing, such as those who have depressed consciousness, respiratory tract instrumentation

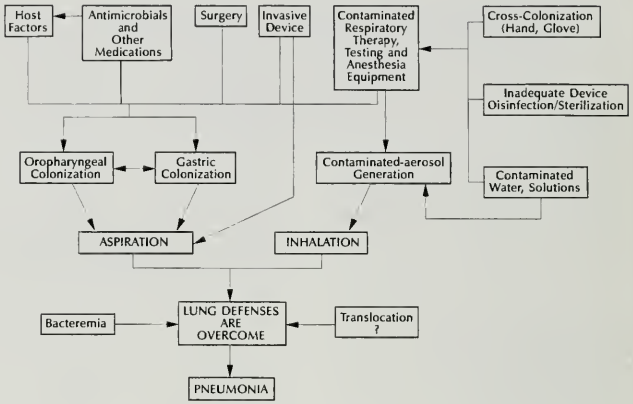

Fig 1. Pathogenesis of nosocomial bacterial pneumonia.

and/or mechanically assisted ventilation, or gastrointestinal tract instrumentation or diseases, or who have just undergone surgery, are particularly likely to aspirate.[6,34,35,63,85-87]

The high incidence of gram-negative bacillary pneumonia in hospitalized patients appears to be the result of factors that promote colonization of the pharynx by gram-negative bacilli and the subsequent entry of these organisms into the lower respiratory tract.[33,88-91] Whereas aerobic gram-negative bacilli are recovered infrequently or are found in small numbers in pharyngeal cultures of healthy persons,[88,92] colonization dramatically increases in patients with coma, hypotension, acidosis, azotemia, alcoholism, diabetes mellitus, leukocytosis, leukopenia, pulmonary disease, or nasogastric or endotracheal tubes in place, and in patients given antimicrobial agents.[33,91,93,94]

Oropharyngeal or tracheobronchial colonization by gram-negative bacilli begins with the adherence of the microorganisms to the host's epithelial cells.[90,95-97] Adherence may be affected by multiple factors related to the bacteria (presence of pili, cilia, capsule, or production of elastase or mucinase), host cell (surface proteins and polysaccharides), and environment (pH and presence of mucin in respiratory secretions).[89,90,95,98-107] The exact interactions among these factors have not been fully elucidated, but studies indicate that certain substances, such as fibronectin, can inhibit the adherence of gram-negative bacilli to host cells.[98,100,108] Conversely, certain conditions, such as malnutrition, severe illness, or postoperative state, can increase adherence of gram-negative bacteria.[89,98,102,107,109]

Besides the oropharynx, the stomach has been postulated to be an important reservoir of organisms that cause nosocomial pneumonia.[34,110-114] The stomach's role may vary depending on the patient's underlying conditions and on prophylactic or therapeutic interventions.[22,111,115-118] In healthy persons, few bacteria entering the stomach survive in the presence of hydrochloric acid at pH < 2.[119,120] However, when gastric pH increases from the normal levels to ≥ 4, microorganisms are able to multiply to high concentrations in the stomach.[117,119,121-123] This can occur in patients with advanced age,[121] achlorhydria,[119] ileus, or upper gastrointestinal disease, and in patients receiving enteral feeding, antacids, or histamine-2 (H-2) antagonists.[111,117,118,123-125] The contribution of other factors, such as duodeno-gastric reflux and the presence of bile, to gastric colonization in patients with impaired intestinal motility has been suggested and needs further investigation.[116]

Bacteria can also gain entry into the lower respiratory tract of hospitalized patients through inhalation of aerosols generated primarily by contaminated respiratory therapy or anesthesia breathing equipment.[126-129]

Outbreaks related to the use of respiratory therapy equipment have been associated with contaminated nebulizers, which are humidification devices that produce large amounts of aerosol droplets < 4 μm via ultrasound, spinning disk, or the Venturi mechanism.[126,129,130] When the fluid in the reservoir of a nebulizer becomes contaminated with bacteria, the aerosol produced may contain high concentrations of bacteria that can be deposited deep in the patient's lower respiratory tract.[126,130,131] Because endotracheal and tracheal tubes provide direct access to the lower respiratory tract, contaminated aerosol inhalation is particularly hazardous for intubated patients. In contrast to nebulizers, bubble-through or wick humidifiers mainly increase the water-vapor (or molecular-water) content of inspired gases. Although heated bubble-through humidifiers generate aerosol droplets, they do so in quantities that may not be clinically significant;[127,132] wick humidifiers do not generate aerosols.

Rarely, bacterial pneumonia can result from hematogenous spread of infection to the lung from another infection site, eg, pneumonia resulting from purulent phlebitis or right-sided endocarditis. Another mechanism, translocation of bacteria via the passage of viable bacteria from the lumen of the gastrointestinal tract through epithelial mucosa to the mesenteric lymph nodes and to the lung, has been shown in animal models.[133] Translocation is postulated to occur in patients with immunosuppression, cancer, or burns;[133] however data are lacking regarding this mechanism in humans.[134]

V. Risk Factors and Control Measures

Several large studies have examined potential risk factors for nosocomial bacterial pneumonia (Table 2).[6,34,35,135,136] Although specific risk factors may differ between study populations, they can be grouped into the following general categories: (1) host factors such as extremes of age and severe underlying conditions, including immunosuppression; (2) factors, such as administration of antimicrobials, admission to the ICU, underlying chronic lung disease, or coma, that enhance colonization of the oropharynx and/or stomach by microorganisms; (3) conditions favoring aspiration or reflux, including endotracheal intubation, insertion of nasogastric tube, or supine position; (4) conditions requiring prolonged use of mechanical ventilatory support with potential exposure to contaminated respiratory equipment and/or contact with contaminated or colonized hands of health-care workers; and (5) factors that impede adequate pulmonary toilet, such as surgical procedures involving the head, neck, thorax, or upper abdomen, and immobilization due to trauma or illness.[6,33-35,62,73,74,135]

A. Oropharyngeal, Tracheal, and Gastric Colonization

The association between colonization of the oropharynx,[88,137] trachea,[138] or stomach[110,111,117,123] and predisposition to gram-negative bacillary pneumonia prompted attempts to prevent infection either by prophylactic local application of antimicrobial agent(s)[139,140] or by utilizing the phenomenon of local bacterial interference.[141,142] Although early work suggested that the former method, use of aerosolized antimicrobials, could eradicate common gram-negative pathogens from the upper respiratory tract,[138] superinfection occurred in some patients receiving this therapy.[139-141,143,144] The latter method, bacterial interference (with alpha-hemolytic streptococci), has been successfully used by some investigators to prevent oropharyngeal colonization by aerobic gram-negative bacilli.[141] However, the efficacy of this method for use in general has not been evaluated.

The administration of antacids and H2-blockers for prevention of stress bleeding in critically ill, postoperative, and/or mechanically ventilated patients has been associated with gastric bacterial overgrowth in many studies.[34,112,113,118,122,123,145-147] Sucralfate, a cytoprotective agent that has little effect on gastric pH and may have bactericidal properties of its own, has been suggested as a potential substitute for antacids and H-2 blockers.[148-150] The results of clinical trials comparing the risk of pneumonia in patients receiving sucralfate to that in patients given antacids and/or H-2 blockers have been variable.[112,118,147,148,151-153] In most randomized trials, ICU patients receiving mechanically assisted ventilation and antacids with or without H-2 blockers had increased gastric pH, high bacterial counts in the gastric fluid, and increased risk of pneumonia compared with patients given sucralfate.[112,118,147,148,151] In one report with a large number of study patients, the incidence of early-onset pneumonia (occurring ≤ 4 days after intubation) did not differ between patient groups, but late-onset pneumonia occurred in 5% of 76 patients who received sucralfate, 16% of 69 given antacids, and 21% of 68 who received an H-2 blocker.[147] On the other hand, a meta-analysis of data from eight earlier studies[154] and a later study comparing sucralfate with ranitidine[153] did not show a strong association between nosocomial pneumonia and drugs that raise gastric pH. Further comparative studies are under way in which bronchoscopy with PSB or BAL is utilized for the diagnosis of pneumonia.

Selective decontamination of the digestive tract (SDD) is another strategy designed to prevent bacterial colonization and lower respiratory tract infection in mechanically ventilated patients.[155-179] SDD is aimed at preventing oropharyngeal and gastric colonization with aerobic gram-negative bacilli and *Candida* spp., without altering the anaerobic flora (Table 3). A variety of SDD regimens use a combination of locally administered nonabsorbable antibiotic agents such as polymyxin and an aminoglycoside (tobramycin, gentamicin, or, rarely, neomycin) or a quinolone (norfloxacin or ciprofloxacin), coupled with either amphotericin B or nystatin. The local antimicrobial preparation is applied as a paste to the oropharynx and given orally or via the nasogastric tube four times a day. In addition, in many studies, a systemic (intravenous) antimicrobial such as cefotaxime or trimethoprim is administered to the patient.

While most clinical trials,[155-158,160-167,169,170,175-177] including two meta-analyses,[171,178] of SDD have demonstrated a decrease in the rates of nosocomial respiratory infections, these trials have been difficult to assess because they have differed in study design and population, and many have had short follow-up periods (Table 3). In most of these studies, the diagnosis of pneumonia was based on clinical criteria; bronchoscopy with BAL or PSB was used in only a few studies.[159,162,173,175-177,179]

Two recently published large double-blind, placebo-controlled trials demonstrated no benefit from SDD.[173,174] In one, a large French multicenter study by Gastinne et al, a significant decrease in incidence of gram-negative bacillary pneumonia was not accompanied by a decrease in pneumonia from all causes.[173] In the other study, by Hammond et al, no differences were noted between patients randomized to SDD or to placebo; however, both patient groups received intravenous cefotaxime.[174]

Table 2. Risk Factors and Suggested Infection Control Measures for Prevention of Nosocomial Pneumonia

Risk Factors	Infection Control Measures Suggested to Prevent Nosocomial Pneumonia
Bacterial Pneumonia	
Host-Related Age >65 Years	
Underlying illness:	
Chronic Obstructive Pulmonary Disease (COPD)	Perform incentive spirometry; positive end expiratory pressure or continuous positive airway pressure by face mask.
Immunosuppression	Avoid exposure to potential nosocomial pathogens; decrease duration of immunosuppression, such as by administration of granulocyte macrophage colony stimulating factor (GMCSF).
Depressed consciousness	Administer central nervous system depressants cautiously.
Surgery (thoracic/abdominal)	Properly position patients; promote early ambulation; appropriately control pain.
Device-Related	Properly clean, sterilize or disinfect, and handle devices; remove devices as soon as the indication for their use ceases.
Endotracheal intubation and mechanical ventilation	Gently suction secretions; place patient in semirecumbent position, ie, 30° to 45° head-elevation; use nonalkalinizing gastric cytoprotective agent on patients at risk for stress bleeding; do not routinely change ventilator circuits more often than every 48 hours; drain and discard inspiratory-tubing condensate, or use heat-moisture exchanger if indicated.
Nasogastric tube (NGT) placement and enteral feeding	Routinely verify appropriate tube placement; promptly remove NGT when no longer needed. Drain residual; place patient in semirecumbent position as described above.
Personnel- or Procedure-Related	
Cross-contamination by hands	Educate and train personnel; wash hands adequately and wear gloves appropriately; conduct surveillance for cases of pneumonia, and give feedback to personnel.
Antibiotic administration	Use antibiotics prudently, especially on high-risk intensive-care unit (ICU) patients.
Legionnaires' Disease	
Host-Related	
Immunosuppression	Decrease duration of immunosuppression.
Device-Related	
Contaminated aerosol from devices	Sterilize/disinfect aerosol-producing devices before use; use only sterile water for respiratory humidifying devices; do not use cool-mist room-air "humidifiers" without adequate sterilization or disinfection.
Environment-Related	
Aerosols from contaminated water supply	Hyperchlorinate or superheat hospital water system; routinely maintain water-supply system; consider use of sterile water for drinking by immunosuppressed patients.
Cooling-tower draft	Properly design, place, and maintain cooling towers.
Aspergillosis	
Host-Related	
Severe granulocytopenia	Decrease duration of immunosuppression, such as by administration of GMCSF; place patients with severe and prolonged granulocytopenia in protected environment.
Environment-Related	
Construction activity	Remove granulocytopenic patients from vicinity of construction; if not already done, place severely granulocytopenic patients in protected environment; make severely granulocytopenic patients wear a mask when they leave their protected environment.
Other environmental sources of aspergilli	Routinely maintain hospital air-handling system and rooms of immunosuppressed patients.
Respiratory Syncytial Virus Infection	
Host-Related	
Age <2 Years; Congenital Pulmonary/Cardiac Disease, Immunosuppression	Consider routine preadmission screening of patients at high-risk for severe RSV infection, followed by cohorting of patients and nursing personnel during hospital outbreaks of RSV infection.
Personnel- or Procedure-Related	
Cross-contamination by hands	Educate personnel; wash hands; wear gloves; wear a gown; during outbreaks, use private rooms or cohort patients and nursing personnel, and limit visitors.
Influenza	Place infected patients in private rooms or cohort them.
Host-Related	
Age >65 years; Immunosuppression	Vaccinate high-risk patients before the influenza season each year; use amantadine or rimantadine for chemoprophylaxis during an outbreak.
Personnel-Related	
Infected personnel	Before the influenza season each year, vaccinate personnel caring for high-risk patients; use amantadine or rimantadine for prophylaxis during an outbreak.

Table 3. Controlled Studies on Nosocomial Lower Respiratory Tract Infections and Other Associated Outcomes of Selective Decontamination of the Digestive Tract in Adult Patients with Mechanically Assisted Ventilation

Author	Study Patients	Lower Respiratory Tract Infection: Diagnostic Method	Lower Respiratory Tract Infection: Infection Rate SDD[D] (%)	Lower Respiratory Tract Infection: Infection Rate Controls (%)	Colonization or Infection with Resistant[A] Microorganisms[B] SDD[D] (%)	Colonization or Infection with Resistant[A] Microorganisms[B] Controls (%)	Overall Mortality In Hospital SDD[D] (%)	Overall Mortality In Hospital Controls (%)	Mean Total Number of Days in ICU[C] SDD[D]	Mean Total Number of Days in ICU[C] Controls
Stoutenbeek[155] (1984)	Trauma; SDD = 63; controls = 59	Clinical & radiologic;[F] TS culture[F]	8	59	"No increase"		3	8	Not reported	
Unertl[156] (1987)	General ICU; SDD = 19; controls = 20	Clinical & radiologic[E]	21	70	21[G]	20[G]	26	30	18[H]	23[H]
Kerver[157] (1988)	Surgical ICU; SDD = 49; controls = 47	Clinical & radiologic[E]	12	85	"Not recorded"		29; IR[I] = 4	32; IR[I] = 17	17	20
Ledingham[158] (1988)	General ICU; SDD = 163; controls = 161	Clinical & radiologic[E]	2	11	"No increase"		24	24	Not reported	
Brun-Buisson[159] (1989)	Medical ICU; SDD = 36; controls = 50	Clinical & radiologic;[F] TS & PSB culture[F]	20	22	3[G]	16[G]	22; IR[I] = 9	24; IR[I] = 10	14	15
Ulrich[160] (1989)	General ICU; SDD = 48; controls = 52	Clinical & radiologic;[F] TS culture[F]	15	50	GP = 78[J] GN = 3[J]	GP = 44[J] GN = 2[J]	31; IR[I] = 0	54; IR[I] = 15	17	13
Flaherty[161] (1990)	Cardiac surgery ICU; SDD = 51; controls = 56	Clinical & radiologic[E]	2	9	GN = 22[G]	GN = 21[G]	0	2	Not reported	
Godard[162] (1990)	General ICU; SDD = 97; controls = 84	Clinical & radiologic;[F] TS & PSB culture[F]	2	15	GN = 15[J]	GN = 15[J]	12	18	11	16
McClelland[163] (1990)	Renal & respiratory failure; SDD = 15; controls = 12	TS culture[F]	7	50	Not reported		60; IR[I] = 27	58; IR[I] = 8	Not reported	
Rodriquez-Roldan[164] (1990)	General ICU; SDD = 13; controls = 15	Clinical & radiologic;[F] TS culture[F]	Pn = 0[K] TB = 23[K]	Pn = 73[K] TB = 20[K]	"None noticed"		30; IR[I] = 0	33; IR[I] = 13	Not reported	
Tetteroo[165] (1990)	Esophageal resection; SDD = 56; controls = 56	Clinical & radiologic;[F] culture of bronchial aspirate	2	14	2[G]	4[G]	5; IR[I] = 4	4; IR[I] = 0	6	5
Aerdts[166] (1991)	General ICU; SDD = 17; controls-A = 18[L]; controls-B = 21[L]	Clinical & radiologic;[F] TS culture[F]	6	A = 78; B = 62	"Not Observed"		12; IR[I] = 6	A = 22; IR[I] = 11; B = 10; IR[I] = 0	23	A = 30; B = 25
Blair[167] (1991)	General ICU; SDD = 126; controls = 130	Clinical & radiologic[E]	10	35	"No evidence of increased resistance"		14	19	8	8
Fox[168] (1991)	Cardiac bypass; SDD = 12; controls = 12	TS culture[F]	66	50	Not reported		17	66	12	12
Hartenauer[169] (1991)	Surgical ICU *ICU-1*: SDD = 50; controls = 61	Clinical & radiologic;[F] TS culture[F]	10	46	S = 34[G]; GN = 0[G]	S = 33[G]; GN = 0[G]	38 IR[I] = 8	35; IR[I] = 21	12	13
	ICU-2: SDD = 49; controls = 40		10	45	S = 37;[G] GN = 0[G]	S = 37;[G] GN = 0[G]	31; IR[I] = 6	43; IR[I] = 25	13	17

Table 3 (continued) Controlled Studies on Nosocomial Lower Respiratory Tract Infections and Other Associated Outcomes of Selective Decontamination of the Digestive Tract in Adult Patients with Mechanically Assisted Ventilation

Author	Study Patients	Lower Respiratory Tract Infection: Diagnostic Method	Lower Respiratory Tract Infection: Infection Rate SDD[D] (%)	Lower Respiratory Tract Infection: Infection Rate Controls (%)	Colonization or Infection with Resistant[A] Microorganisms[B] SDD[D] (%)	Colonization or Infection with Resistant[A] Microorganisms[B] Controls (%)	Overall Mortality In Hospital SDD[D] (%)	Overall Mortality In Hospital Controls (%)	Mean Total Number of Days in ICU[C] SDD[D]	Mean Total Number of Days in ICU[C] Controls
Pugin[170] (1991)	Surgical ICU; SDD = 25; controls = 27	Clinical & radiologic;[E] TS culture[F]	16	78	"No new antibiotic resistance"		28	26	13	15
Vandenbroucke-Grauls[171] (1991)	ICUs (pooled data);[M] *SDD-A* = 488; controls-A (historical) = 540; *SDD-B* = 225; controls-B (random) = 266	Clinical & radiologic;[E] TS culture[F]	A = 7; B = 8	A = 28; B = 45	"No increase in resistant microorganisms in 10 of 11 studies"		A = 25; B = 21	A = 26; B = 26	Not reported	
Cockerill[172] (1992)	Surgical and medical ICUs; SDD = 75; controls = 75	Clinical & radiologic;[E] TS culture[F]	Pn = 5[K]; TB = 4[K]	Pn = 16[K]; TB = 5[K]	16[J]	11[J]	15	21	10	12
Gastinne[173] (1992)	Medical ICU; SDD = 220; controls = 225	Clinical & radiologic;[E] TS ± PSB culture[F]	12	15	Not reported		40; 34[N]	36; 34[N]	18	19
Hammond[174] (1992)	General ICU; SDD = 114; controls = 125	Clinical & radiologic;[E] TS culture[F]	Pn = 15;[K] Br = 6[K]	Pn = 15;[K] Br = 6[K]	Not reported[O]		18; IR[I] = 6	17; IR[I] = 6	16	17
Rocha[175] (1992)	General ICU; SDD = 47; controls = 54	Clinical & radiologic;[E] TS ± BAL culture[F]	26	63	GP = 62;[J] GN = 43[J]	GP = 38;[J] GN = 30[J]	21; IR[I] = 2	44; IR[I] = 20	19	18
Winter[176] (1992)	General ICU; SDD = 91; *control-A* = 84; *control-B* = 92	Clinical & radiologic;[E] BAL culture[F]	3	A = 11; B = 23	1-8[J]	A = 1-7;[J] B = 1-17[J]	36	A = 43; B = 43	6	A = 7; B = 8
Korinek[177] (1993)	Neurosurgical ICU; SDD = 63; controls = 60	Clinical & Radiologic;[E] TS & PSB culture[F]	24	42	"No evidence of increased resistance"		8	7	24	29
SDD Trialists[178] (1993)	ICUs (pooled data);[M] SDD = 2047; controls = 2095	Variable	Odds ratio = 0.37;[P] CI_{95}[Q], 0.31-0.43		Not analyzed		27 Odds ratio = 0.90; CI_{95}[Q], 0.79-1.04	29	Not analyzed	
Ferrer[179] (1994)	Respiratory ICU; SDD = 39; controls = 41	Clinical & radiologic;[E] TS + PSB or BAL culture[F] ± autopsy histology	18	24	Not reported[R]		31	27	Not reported	

[A] Resistant to at least one antimicrobial in the SDD regimen
[B] During the study period
[C] ICU = intensive care unit
[D] SDD = selective digestive tract decontamination
[E] Clinical criteria included temperature > 38°C, purulent bronchorrhea, WBC > (12,000-15,000/mm³). Radiologic criterion was evidence of new and progressive infiltrate(s)
[F] TS = tracheal secretions; PSB = protected-specimen brushing; BAL = broncho-alveolar lavage
[G] Percentage of patients infected or colonized with gram-positive (GP) and/or gram-negative bacillary (GN) organisms at any body site; GP = percentage of patients infected or colonized with gram-positive organisms at any body site; GN = percentage of patients infected or colonized with gram-negative bacillary organisms at any body site; S = Percentage of patients with coagulase-negative staphylococcal infection or colonization
[H] Median
[I] IR = Infection-related
[J] Percentage of isolates; GP = percentage of gram-positive isolates; GN = percentage of gram-negative bacillary isolates
[K] Pn = pneumonia, TB = tracheo-bronchial infection; Br = bronchial infection
[L] Control-A = patients given penicillin (ampicillin, piperacillin, or flucloxacillin) for clinical infection(s), Control-B = patients given cephalosporin (cephadrine, cefuroxime, or cefotaxime) for clinical infection(s)
[M] Meta-analysis
[N] In ICU
[O] However, at 4 weeks, 13% and 5%, respectively, of oropharyngeal cultures of SDD and control patients had MRSA, and 41% of SDD and control patients were colonized with enterococci
[P] Computed using data from 3,836 patients and 526 events, 260 in SDD- and 366 in control-patients
[Q] CI_{95} = 95% confidence interval
[R] However, MRSA bronchial colonization occurred in 45% of SDD patients and 21% of controls

Although an earlier meta-analysis suggested a trend toward decreased mortality in patients given SDD,[171] a more recent and more extensive analysis highlights the equivocal effect of SDD on patient mortality, as well as the high cost of using SDD to prevent pneumonia or death (ie, in order to prevent one case of nosocomial pneumonia, or one death due to nosocomial pneumonia, 6 [range: 5-9] or 23 [range: 13-39] patients, respectively, would have to be given SDD).[178] Furthermore, there are concerns over the development of antimicrobial resistance and superinfection with gram-positive bacteria and other antibiotic-resistant nosocomial pathogens.[156,158,159,161,175,180] Thus, currently available data do not justify the routine use of SDD for prevention of nosocomial pneumonia in ICU patients. SDD may be ultimately useful for specific subsets of ICU patients, such as those with trauma or severe immunosuppression, eg, bone-marrow transplant recipients.

A new approach advocated to prevent oropharyngeal colonization in patients receiving enteral nutrition is to reduce bacterial colonization of the stomach by acidifying the enteral feed.[181] Although the absence of bacteria from the stomach has been confirmed in patients given acidified enteral feeding, the effect on the incidence of nosocomial pneumonia has not been evaluated.[181]

B. Aspiration of Oropharyngeal and Gastric Flora

Clinically significant aspiration usually occurs in patients who have one or more of the following conditions: a depressed level of consciousness; dysphagia due to neurologic or esophageal disorders; an endotracheal (naso- or orotracheal), tracheostomy, or enteral (naso- or orogastric tube) in place, and receipt of enteral feeding.[35,84,85,182-186] Placement of an enteral tube may increase nasopharyngeal colonization, cause reflux of gastric contents, or allow bacterial migration via the tube from the stomach to the upper airway.[183,186-188] When enteral feedings are administered, gross contamination of the enteral solution during preparation[189-191] and elevated gastric pH[70,192,193] may lead to gastric colonization with gram-negative bacilli. In addition, gastric reflux and aspiration may occur because of increased intragastric volume and pressure.[70,117,183]

Prevention of pneumonia in such patients may be difficult, but methods that make regurgitation less likely (for example, placing the patient in a semirecumbent position by elevating the head of the bed and withholding enteral feeding when the residual volume in the stomach is large or if bowel sounds are not heard upon auscultation of the abdomen) may be beneficial.[185,194-197] On the other hand, administering enteral nutrition intermittently in small boluses rather than continuously;[70,193] using flexible, small-bore enteral tubes;[186,198] or placing the enteral tube below the stomach (eg, in the jejunum[199,200]) have yielded equivocal results.

C. Mechanically Assisted Ventilation and Endotracheal Intubation

Patients receiving continuous, mechanically assisted ventilation have 6-21 times the risk of developing nosocomial pneumonia compared with patients not receiving ventilatory support.[34,63,65,75] Data from the study by Fagon and co-workers indicate that the risk of developing ventilator-associated pneumonia increases by 1% per day.[5] This increased risk is partly due to carriage of oropharyngeal organisms upon passage of the endotracheal tube into the trachea during intubation, as well as to depressed host defenses secondary to the patient's severe underlying illness.[6,34,35,201] In addition, bacteria can aggregate on the surface of the tube over time and form a glycocalyx (biofilm) that protects the bacteria from the action of antimicrobial agents or host defenses.[202] Some investigators believe that these bacterial aggregates may become dislodged by ventilation flow, tube manipulation, or suctioning and subsequently embolize into the lower respiratory tract and cause focal pneumonia.[203,204] Removing tracheal secretions by gentle suctioning and using aseptic technique to reduce cross-contamination to patients from contaminated respiratory therapy equipment or contaminated or colonized hands of personnel have been utilized traditionally to help prevent pneumonia in patients receiving mechanically assisted ventilation.

The risk of pneumonia is also increased by the direct access of bacteria to the lower respiratory tract, often because of leakage around the endotracheal tube cuff,[86,205] which allows pooled secretions above the cuff to enter the trachea.[206] In one recent study, the occurrence of nosocomial pneumonia was delayed and decreased in intubated patients whose endotracheal tubes had a separate dorsal lumen that allowed drainage (by suctioning) of secretions in the space above the endotracheal tube cuff and below the glottis.[206] However, further studies are needed to determine the cost-benefit ratio of using this device.

D. Cross-Colonization Via Hands of Personnel

Pathogens causing nosocomial pneumonia, such as gram-negative bacilli and *Staphylococcus aureus*, are ubiquitous in the hospital, especially in intensive or critical care areas.[207,208] Transmission of these microorganisms to patients frequently occurs via health-care workers' hands that become contaminated or transiently colonized with the microorganisms.[209-215] Procedures such as tracheal suctioning and manipulation of ventilator circuit or endotracheal tubes increase the opportunity for cross-contamination.[215,216] The risk of cross-contamination can be reduced by using aseptic technique and sterile or disinfected equipment when appropriate[65] and by eliminating pathogens from the hands of personnel.[65,215,217-219]

In theory, adequate handwashing is an effective way of removing transient bacteria from the hands,[218,219] but personnel compliance with handwashing has been generally poor.[220-223] For this reason, the routine use of gloves has been advocated to help prevent cross-contamination.[224,225] Routine gloving (in addition to gowning) was associated with a decrease in the incidence of nosocomial respiratory syncytial virus (RSV)[226] and other ICU infections.[227] However, nosocomial pathogens can colonize gloves,[228] and outbreaks have been traced to health-care workers who did not change gloves after contact with one patient and before providing care to another.[229,230] In addition, gloved hands may get contaminated via leaks in the gloves.[231]

E. Contamination of Devices Used on the Respiratory Tract

Devices used on the respiratory tract for respiratory therapy (eg, nebulizer), diagnostic examination (eg, bronchoscope or spirometer), or administration of anesthesia are potential reservoirs or vehicles for infectious microorganisms.[65,232-236] Routes of transmission may be from device to patient,[127,129,234-244] from one patient to another,[245,246] or from one body site to the

lower respiratory tract of the same patient via hand or device.[233,246-248] Contaminated reservoirs of aerosol-producing devices, eg, nebulizers, can allow the growth of hydrophilic bacteria that may be subsequently aerosolized during device use,[126,129,130,242] Gram-negative bacilli such as *Pseudomonas* spp., *Xanthomonas* spp., *Flavobacterium* spp., *Legionella* spp., and nontuberculous mycobacteria can multiply to substantial concentrations in nebulizer fluid[241,249-251] and increase the device-user's risk of acquiring pneumonia.[127-130,241,242,252,253]

Proper cleaning and sterilization or disinfection of reusable equipment are important components of a program to reduce infections associated with respiratory therapy and anesthesia equipment.[234,235,237-240,242,254-259] Many devices or parts of devices used on the respiratory tract have been categorized as semicritical in the Spaulding classification system for appropriate sterilization or disinfection of medical devices because they come into direct or indirect contact with mucous membranes but do not ordinarily penetrate body surfaces (See Appendix A), and the associated infection risk following the use of these devices in patients is less than that associated with devices that penetrate normally sterile tissues.[260] Thus, if it is not possible or cost-effective to sterilize these devices by steam autoclave or ethylene oxide,[261] they can be subjected to high-level disinfection by pasteurization at 75°C for 30 min,[262-265] or by using liquid chemical disinfectants approved by the Environmental Protection Agency (EPA) as sterilants/disinfectants and cleared for marketing for use on medical instruments by the Food and Drug Administration.[225,266-268]

When rinsing is needed (to remove residual liquid chemical sterilant/disinfectant) after a respiratory device has been chemically disinfected, sterile water has been preferred because tap or locally prepared distilled water may harbor microorganisms that can cause pneumonia.[249,250,269-272] In some hospitals, a tap-water rinse followed by air-drying with or without an alcohol rinse (to hasten drying) is used.[273] In theory, if complete drying is achieved following a tap-water rinse, the risk of nosocomial pneumonia associated with the use of the device is probably low. Drying has been shown to lower the level of microbial contamination of gastrointestinal endoscopes and washed hands.[274-276] However, many semicritical items used on the respiratory tract (eg, corrugated tubing, jet or ultrasonic nebulizers, bronchoscopes) are difficult to dry and the degree of dryness of a device is difficult to assess.[265] Data are lacking regarding the safety of routinely using tap water for rinsing (followed by drying) reusable semicritical respiratory devices after their disinfection or between their uses on the same patient.[242,258,273,277]

1. Mechanical Ventilators, Breathing Circuits, Humidifiers, Heat-Moisture Exchangers and In-Line Nebulizers

a. *Mechanical ventilators.* The internal machinery of mechanical ventilators used for respiratory therapy is not considered an important source of bacterial contamination of inhaled gas.[278] Thus, routine sterilization or high-level disinfection of the internal machinery is considered unnecessary. Using high-efficiency bacterial filters at various positions in the ventilator breathing circuit had been advocated previously.[279,280] Filters interposed between the machinery and the main breathing circuit can eliminate contaminants from the driving gas and prevent retrograde contamination of the machine by the patient but may also alter the functional specifications of the breathing device by impeding high gas flows.[279-281] Placement of a filter or condensate trap at the expiratory-phase tubing of the mechanical- ventilator circuit may help prevent cross-contamination of the ventilated patient's immediate environment,[247,282] but the importance of such filters in preventing nosocomial pneumonia needs further evaluation.

b. *Breathing circuits, humidifiers, and heat-moisture exchangers.* Most U.S. hospitals currently use ventilators with either bubble-through or wick humidifiers that produce either insignificant[132,283] or no aerosols, respectively, for humidification. Thus, they do not seem to pose an important risk for pneumonia in patients. In addition, bubble-through humidifiers are usually heated to temperatures that reduce or eliminate bacterial pathogens.[283,284] Sterile water, however, is still generally used to fill these humidifiers[285] because tap or distilled water may harbor microorganisms, such as *Legionella* spp., that are more heat-resistant than other bacteria.[252,271]

The potential risk for pneumonia in patients using mechanical ventilators with heated bubble-through humidifiers stems primarily from the condensate that forms in the inspiratory-phase tubing of the ventilator circuit as a result of the difference in the temperatures of the inspiratory-phase gas and ambient air; condensate formation increases if the tubing is unheated.[286] The tubing and condensate can rapidly become contaminated, usually with bacteria that originate from the patient's oropharynx.[286] In the study by Craven et al, 33% of inspiratory circuits were colonized with bacteria from patients' oropharynx within 2 hours and 80% within 24 hours of use.[286] Spillage of the contaminated condensate into the patient's tracheobronchial tree, as can occur during procedures in which the tubing may be moved (eg, suctioning, adjusting the ventilator setting, or feeding or caring for the patient), may increase the risk of pneumonia in the patient.[286] Thus, in many hospitals, health-care workers are trained to prevent such spillage and to drain the fluid periodically. Microorganisms contaminating ventilator-circuit condensate can be transmitted to other patients via hands of the health-care worker handling the fluid, especially if the health-care worker fails to wash his or her hands after handling the condensate.

The role of ventilator-tubing changes in preventing pneumonia in patients using mechanical ventilators with bubble-through humidifiers has been investigated. Initial studies of in-use contamination of mechanical ventilator circuits with humidifiers have shown that neither the rate of bacterial contamination of inspiratory-phase gas nor the incidence of pneumonia was significantly increased when tubing was changed every 24 hours rather than every 8 or 16 hours.[287] Craven et al later showed that changing the ventilator circuit every 48 hours rather than 24 hours did not result in an increase in contamination of the inspiratory-phase gas or tubing of the ventilator circuits.[288] In addition, the incidence of nosocomial pneumonia was not significantly higher when circuits were changed every 48 hours than when changes were done every 24 hours.[288] More recent reports suggest that the risk of pneumonia may not increase when the interval for circuit change is prolonged beyond 48 hours. Dreyfuss and others showed that the risk of pneumonia (8 [29%] of 28) was not significantly higher when the circuits were never changed for the duration of use by the patient, than (11 [31%] of 35) when the circuits were changed every 48 hours.[289]

These findings indicate that the recommended daily change in ventilator circuits may be extended to ≥ 48 hours. This change

in recommendation is expected to result in large savings in device use and personnel time for U.S. hospitals.[285,288] The maximum time, however, that a circuit can be safely left unchanged on a patient has yet to be determined.

Condensate formation in the inspiratory-phase tubing of a ventilator breathing circuit can be decreased by elevating the temperature of the inspiratory-phase gas with a heated wire in the inspiratory-phase tubing. However, in one report, three cases of endotracheal- or tracheostomy-tube blockage by dried-up patient secretions were attributed to the decrease in the relative humidity of inspired gas that results from the elevation of the gas temperature.[289] Until further data are available about the frequency of the occurrence of such cases, users of heated ventilator tubing should be aware of the advantages and potential complications of using heated tubing.

Condensate formation can be eliminated by using a heat-moisture exchanger (HME) or a hygroscopic condenser humidifier ("artificial nose").[291-296] An HME recycles heat and moisture exhaled by the patient, and eliminates the need for a humidifier. In the absence of a humidifier, no condensate forms in the inspiratory-phase tubing of the ventilator circuit. Thus, bacterial colonization of the tubing is prevented, and the need to routinely change the tubing periodically is obviated.[216] Some models of HMEs are equipped with bacterial filters, but the advantage of these filters remains unknown. HMEs can increase the dead space and resistance to breathing, may leak around the endotracheal tube, and may result in drying of sputum and blockage of the tracheobronchial tree.[297] Although recently developed HMEs with humidifiers increase airway humidity without increasing colonization with bacteria,[293,298] more studies are needed to determine whether the incidence of pneumonia is decreased.[299-302]

c. *Small-Volume ("In-Line") Medication Nebulizers.* Small-volume medication nebulizers that are inserted in the inspiratory circuit of mechanical ventilators can produce bacterial aerosols.[242] If they become contaminated by condensate in the inspiratory tubing of the breathing circuit, they can increase the patient's risk of pneumonia because the nebulizer aerosol is directed through the endotracheal tube and bypasses many of the normal host defenses against infection.[296]

2. **Large-Volume Nebulizers**. Nebulizers with large-volume (> 500 cc) reservoirs, including those used in intermittent positive-pressure breathing (IPPB) machines and ultrasonic or spinning-disk room-air "humidifiers," pose the greatest risk of pneumonia to patients, probably because of the total amount of aerosol they generate.[237-241,252,303] These reservoirs can become contaminated by hands of personnel, unsterile humidification fluid, or inadequate sterilization or disinfection between uses.[126] Once introduced into the reservoir, various bacteria, including *Legionella* spp., can multiply to sufficiently large numbers within 24 hours to pose a risk of infection in patients who receive inhalation therapy.[128,129,241,253,303] Sterilization or high-level disinfection of these nebulizers can eliminate vegetative bacteria from their reservoirs and make them safe for patient use.[241] Unlike nebulizers attached to IPPB machines, however, room-air "humidifiers" have a high cost-benefit ratio: evidence of clinical benefits from their use in hospitals is lacking, and the potential cost of daily sterilization or disinfection of, and use of sterile water to fill, such devices is substantial.

3. **Hand-Held Small-Volume Medication Nebulizers.** Small-volume medication nebulizers for administration of bronchodilators, including those that are hand-held, can produce bacterial aerosols. Hand-held nebulizers have been associated with nosocomial pneumonia, including Legionnaires' disease, resulting from contamination with medications from multidose vials[304] or Legionella-contaminated tap water used for rinsing and filling the reservoir.[258]

4. **Suction Catheters, Resuscitation Bags, Oxygen Analyzers, and Ventilator Spirometers.** Tracheal suction catheters can introduce microorganisms into a patient's lower respiratory tract. Currently, there are two types of suction-catheter systems used in U.S. hospitals, the open single-use catheter system and the closed multi-use catheter system. Studies comparing the two systems have involved small numbers of patients; results suggest that the risk of catheter contamination or pneumonia is not different between patients on whom the single-use suction method is used and those on whom the closed multi-use catheter system is used.[305-307] While advantages of cost and decreased environmental contamination have been attributed to the use of the closed-suction system,[308,309] larger studies are needed to weigh the advantages and disadvantages of one system over the other.[310]

Reusable resuscitation bags are particularly difficult to clean and dry between uses; microorganisms in secretions or fluid left in the bag may be aerosolized and/or sprayed into the lower respiratory tract of the patient on whom the bag is used; in addition, contaminating microorganisms may be transmitted from one patient to another via hands of staff members.[311-313] Oxygen analyzers and ventilator spirometers have been associated with outbreaks of gram-negative respiratory tract colonization and pneumonia resulting from patient-to-patient transmission of organisms via hands of personnel.[233,245] These devices require sterilization or high-level disinfection between uses on different patients. Education of physicians, respiratory therapists, and nursing staff regarding the associated risks and appropriate care of these devices is essential.

5. **Anesthesia Equipment**. The contributory role of anesthesia equipment in outbreaks of nosocomial pneumonia were reported before hospitals implemented routine after-use cleaning and disinfection/sterilization of reusable anesthesia-equipment components that may become contaminated with pathogens during use.[314,315]

a. *Anesthesia machine.* The internal components of anesthesia machines, which include the gas sources and outlets, gas valves, pressure regulators, flowmeters, and vaporizers, are not considered an important source of bacterial contamination of inhaled gases.[316] Thus, routine sterilization or high-level disinfection of the internal machinery is considered unnecessary.

b. *Breathing system or patient circuit.* The breathing system or patient circuit, through which inhaled and/or exhaled gases flow to and from a patient (and may include the tracheal tube or face mask; inspiratory and expiratory tubing; Y-piece; CO_2 absorber and its chamber; the anesthesia ventilator bellows and tubing; humidifier; adjustable pressure-limiting valve; and other devices and accessories), can become contaminated with microorganisms that may originate from the patient's oropharynx or trachea. Recommendations for in-use care, maintenance, and reprocessing (ie, cleaning and disinfection or sterilization) of these components of the breathing system have been published.[317,318] In general, reusable components that directly touch a patient's mucous membranes (eg, face

mask or tracheal tube) or become readily contaminated with a patient's respiratory secretions (eg, Y-piece, inspiratory and expiratory tubing, and attached sensors) are cleaned and subjected to high-level disinfection or sterilization between patients. The other parts of the breathing system (eg, carbon dioxide absorber and its chamber), for which an appropriate and cost-effective schedule of reprocessing has not been firmly determined,[319] are changed, cleaned, and sterilized or subjected to high-level disinfection periodically, according to published guidelines[317,318] and/or their manufacturers' instructions.

Using high-efficiency bacterial filters at various positions in the patient circuit, eg, at the Y-piece or on the inspiratory and expiratory sides of the patient circuit, has been advocated[1,317,320,321] and shown to decrease contamination of the circuit.[321-323] However, the use of bacterial filters to prevent nosocomial pulmonary infections has not been shown effective and needs further study.[324-326]

6. Pulmonary Function Testing Apparatus

a. *Internal parts of pulmonary function testing apparatus.* In general, the internal parts of pulmonary function testing apparatus are not considered an important source of bacterial contamination of inhaled gas.[327] However, because of concern about possible carry-over of bacterial aerosols from an infectious patient- user of the apparatus to the next patient,[246,328] placement of bacterial filters (that remove exhaled bacteria) between the patient and the testing equipment has been recently advocated.[246,329] More studies are needed to evaluate the need for and efficacy of these filters in preventing nosocomial pneumonia.[330]

b. *Tubing, rebreathing valves, and mouthpieces.* Tubing, connectors, rebreathing valves, and mouthpieces may become contaminated with patient secretions during use of the pulmonary function testing apparatus. Thus, they are cleaned and subjected to high-level disinfection or sterilization between uses on different patients.

F. Thoracoabdominal Surgical Procedures

Certain patients are at high risk of developing postoperative pulmonary complications, including pneumonia. These persons include those who are more than 70 years of age, are obese, or have chronic obstructive pulmonary disease.[331-334] Abnormal pulmonary function tests (especially decreased maximum expiration flow rate), a history of smoking, the presence of tracheostomy or prolonged intubation, or protein depletion that can cause respiratory-muscle weakness are also risk factors.[62,68,136] Patients who undergo surgery of the head, neck, thorax, or abdomen may suffer from impairment of normal swallowing and respiratory clearance mechanisms as a result of instrumentation of the respiratory tract, anesthesia, or increased use of narcotics and sedatives;[332,335,336] patients who undergo upper abdominal surgery usually suffer from diaphragmatic dysfunction that results in decreased functional residual capacity of the lungs, closure of airways, and atelectasis.[337,338] Interventions aimed at reducing the postoperative patient's risk of pneumonia have been developed.[339] These include deep breathing exercises, chest physiotherapy, use of incentive spirometry, IPPB, and continuous positive airway pressure (CPAP) by face mask.[339-349] Studies evaluating the relative efficacy of these modalities have shown variable results, and have been difficult to compare because of differences in outcome variables assessed, patient populations studied, and study design.[339,341,342,348-350] Nevertheless, many studies have found deep breathing exercises, use of incentive spirometry, and IPPB as advantageous maneuvers, especially in patients with preoperative pulmonary dysfunction.[342,343,345,346,348-350] In addition, control of pain that interferes with cough and deep breathing during the immediate postoperative period has been shown to decrease the incidence of pulmonary complications after surgery; several methods of controlling pain have been used; these include intramuscular or intravenous (including patient-controlled) administration, or regional (eg, epidural) analgesia.[351-358]

G. Other Prophylactic Measures

1. **Vaccination of Patients.** Although pneumococci are not a major cause of nosocomial pneumonia, they have been identified as etiologic agents of serious nosocomial pulmonary infection and bacteremia.[359-361] The following factors render patients at high risk of complications from pneumococcal infections: ≥ 65 years of age, chronic cardiovascular or pulmonary disease, diabetes mellitus, alcoholism, cirrhosis, cerebrospinal fluid leaks, immunosuppression, functional or anatomic asplenia, or HIV infection. Pneumococcal vaccine is effective in preventing pneumococcal disease.[362,363] Because two thirds or more of patients with serious pneumococcal disease have been hospitalized at least once within 5 years before their pneumococcal illness, offering pneumococcal vaccine in hospitals, eg, at the time of patient discharge, should contribute substantially to preventing the disease.[362,364]

2. **Prophylaxis with Systemic Antimicrobial Agents.** Systemic antimicrobial administration has been a prevalent practice in the prevention of nosocomial infections,[365] including pneumonia,[366] especially in patients who are weaned off mechanical ventilators, postoperative, and/or critically ill.[367] However, the efficacy of such practice is questionable and the potential for superinfection, which may result from any antimicrobial therapy, is a problem.[74,91,366-371]

3. **Use of "Kinetic Beds" or Continuous Lateral Rotational Therapy (CLRT) for the Immobilized State.** Use of kinetic beds or CLRT is a maneuver for prevention of pulmonary and other complications from prolonged immobilization or bed rest, such as in patients with acute stroke, critical illness, head injury or traction, blunt chest trauma, and/or mechanically assisted ventilation.[372-377] This involves the use of a bed that turns continuously and slowly (from ≤ 40° for CLRT to ≥ 40° for kinetic therapy) along its longitudinal axis. Among the hypothesized benefits are improved drainage of secretions within the lungs and lower airways, increased tidal volume, and reduction of venous thrombosis with resultant pulmonary embolization.[378-381] However, the efficacy in preventing pneumonia needs further evaluation because studies have yielded variable results.[372-376] In addition, the studies either involved small numbers of patients,[373] lacked adequate randomization,[372] had no clear definition of pneumonia,[372] did not distinguish between community-acquired and nosocomial pneumonia,[373,377] or did not adjust for possible confounding factors such as mechanical ventilation, endotracheal intubation, nasogastric intubation, and enteral feeding.[372]

LEGIONNAIRES' DISEASE

Legionnaires' disease is a multisystem illness, with pneumonia, caused by

Legionella spp. In contrast, Pontiac fever is a self-limited influenza-like illness, without pneumonia, that is associated with *Legionella* spp.[382]

I. Epidemiology

Since identification of the etiologic agent, numerous outbreaks of nosocomial Legionnaires' disease have been reported and have provided the opportunity to study the epidemiology of epidemic legionellosis. In contrast, the epidemiology of sporadic (ie, nonout break-related) nosocomial Legionnaires' disease has not been well elucidated. However, data suggest that when one case is recognized, the presence of additional cases should be suspected. Of 196 cases of nosocomial Legionnaires' disease reported in England and Wales during 1980 to 1992, 69% occurred during 22 nosocomial outbreaks (defined as two or more cases occurring at an institution during a 6-month period).[383] Nine per cent of cases occurred > 6 months before or after a hospital outbreak. Another 13% were in hospitals where other sporadic cases (but no outbreaks) were identified. Only 9% occurred at institutions where no outbreaks or additional sporadic cases were identified.

The overall proportion of nosocomial pneumonias due to *Legionella* spp. in North America has not been determined, although individual hospitals have reported ranges of 0%-14%.[384-386] Because diagnostic tests for *Legionella* spp. infection are not routinely performed on all patients with hospital-acquired pneumonia in most U.S. hospitals, these ranges probably underestimate the incidence of Legionnaires' disease.

Legionella spp. are commonly found in a variety of natural and man-made aquatic environments[387,388] and may enter hospital water systems in low or undetectable numbers.[389,390] Cooling towers, evaporative condensers, heated potable-water-distribution systems within hospitals, and locally produced distilled water can provide a suitable environment for legionellae to multiply. Factors known to enhance colonization and amplification of legionellae in man-made water environments include temperatures of 25-42°C,[392-396] stagnation,[397] scale and sediment,[393] and the presence of certain free-living aquatic amoebae that are capable of supporting intracellular growth of legionellae.[398,399]

A person's risk of acquiring legionellosis following exposure to contaminated water depends on a number of factors, including the type and intensity of exposure and the exposed person's health status.[400-402] Persons with severe immunosuppression or chronic underlying illnesses, such as hematologic malignancy or end-stage renal disease, are at markedly increased risk for legionellosis.[402-405] Persons in the later stages of acquired immunodeficiency syndrome are also probably at increased risk of legionellosis, but data are limited because of infrequent testing of patients.[402] Persons with diabetes mellitus, chronic lung disease, or non-hematologic malignancy, those who smoke cigarettes, and the elderly are at moderately increased risk.[382] Nosocomial Legionnaires' disease has also been reported among patients at children's hospitals.[406,407]

Underlying disease and advanced age are not only risk factors for acquiring Legionnaires' disease but also for dying from the illness. In a multivariate analysis of 3,524 cases reported to CDC from 1980 through 1989, immunosuppression, advanced age, end-stage renal disease, cancer, and nosocomial acquisition of disease were each independently associated with a fatal outcome.[402] The mortality rate among 803 persons with nosocomially acquired cases was 40% compared with 20% among 2,721 persons with community-acquired cases,[402] probably reflecting increased severity of underlying disease in hospitalized patients.

II. Diagnosis

The clinical spectrum of disease due to *Legionella* spp. is broad and ranges from asymptomatic infection to rapidly progressive pneumonia. Legionnaires' disease cannot be distinguished clinically or radiographically from pneumonia caused by other agents,[408,409] and evidence of infection with other respiratory pathogens does not rule out the possibility of concomitant *Legionella* spp. infection.[410-412]

The diagnosis of legionellosis may be confirmed by any one of the following: culture isolation of *Legionella* from respiratory secretions or tissues, or microscopic visualization of the bacterium in respiratory secretions or tissue by immunofluorescent microscopy; and, for legionellosis due to *L pneumophila* serogroup 1, detection of *L pneumophila* serogroup-1 antigens in urine by radioimmunoassay, or observation of a fourfold rise in *L pneumophila* serogroup-1 antibody titer to ≥ 1:128 in paired acute and convalescent serum specimens by use of an indirect immunofluorescent antibody test (IFA).[413,419] A single elevated antibody titer does not confirm a case of Legionnaires' disease because IFA titers ≥ 1:256 are found in 1-16% of healthy adults.[411,414-417]

Because the above tests complement each other, performing each test when Legionnaires' disease is suspected increases the probability of confirming the diagnosis.[418] However, because none of the laboratory tests is 100% sensitive, the diagnosis of legionellosis is not ruled out even if one or more of the tests are negative.[418,419] Of the available tests, the most specific is culture isolation of *Legionella* spp. from any respiratory tract specimen.[420,421]

III. Modes of Transmission

Inhalation of aerosols of water contaminated with *Legionella* spp. is believed to be the primary mechanism of entry of these organisms into a patient's respiratory tract.[382] In several hospital outbreaks, patients were considered to be infected through exposure to contaminated aerosols generated by cooling towers, showers, faucets, respiratory therapy equipment, and room-air humidifiers.[11,241,258,422-428] In other studies, aspiration of contaminated potable water or pharyngeal colonizers has been proposed as the mode of transmission to certain patients.[426,429-431] Person-to-person transmission, however, has not been observed.

IV. Definition of Nosocomial Legionnaires' Disease

The incubation period for Legionnaires' disease is generally 2-10 days;[432] thus, for epidemiologic purposes, in this document and in the accompanying recommendations by the HICPAC, laboratory-confirmed legionellosis that occurs in a patient who has spent ≥ 10 days continuously in the hospital prior to onset of illness is considered *definite* nosocomial Legionnaires' disease, and laboratory-confirmed infection that occurs 2-9 days after hospitalization is *possible* nosocomial infection.

V. Prevention and Control Measures

A. Prevention of Legionnaires' Disease in Hospitals with No Identified Cases (Primary Prevention)

Prevention strategies in health-care facilities with no cases of nosocomial legionellosis have varied by institution, depending on the immunologic status of the patients, the design and construction of the facility, resources available for implementation of prevention strategies, and state and local regulations.

There are at least two schools of thought regarding the most appropriate and cost-effective approach to prevent nosocomial legionellosis, especially in hospitals where no cases or only sporadic cases of the illness are detected. However, a study comparing the cost-benefit ratios of these strategies has not been done.

The first approach is based on periodic, routine culturing of water samples from the hospital's potable water system, for *Legionella* spp.[433,434] When ≥ 30% of the samples obtained are culture-positive for *Legionella* spp., the hospital's potable water system is decontaminated[434] and diagnostic laboratory tests for legionellosis are made available to clinicians in the hospital's microbiology department so that active surveillance for cases can be instituted.[434,435] This approach is based on the premise that no cases of nosocomial legionellosis can occur in the absence of *Legionella* spp. from the potable water system, and, conversely, once *Legionella* spp. are cultured from the water, cases of nosocomial legionellosis may occur.[429,436] Proponents of this strategy indicate that when physicians are informed that the potable water system of the hospital is culture-positive for *Legionella* spp., they are more inclined to conduct the necessary tests for legionellosis.[435] A potential advantage of this approach is the lower cost of culturing a limited number of water samples, if the testing is done infrequently, compared with the cost of routine laboratory diagnostic testing for legionellosis in all patients with nosocomial pneumonia in hospitals that have had no cases of nosocomial legionellosis.

The main argument against this approach is that in the absence of cases, the relationship between the results of water cultures and the risk of legionellosis remains undefined. The bacterium has been frequently present in hospital water systems,[437] often without being associated with known cases of disease.[271,385,438,439] In a study of 84 hospitals in Quebec, 68% were found to be colonized with *Legionella* spp., and 26% were colonized at > 30% of sites sampled; however, cases of Legionnaires' disease were rarely reported from these hospitals.[271] Similarly, at one hospital where active surveillance for legionellosis and environmental culturing for *Legionella* spp. were done, no cases of legionellosis occurred in a urology ward during a 3.5-month period when 70% of water samples from the ward were culture-positive for *L pneumophila* serogroup 1.[385] Interpretation of the results of routine culturing of water may be confounded by variable culture results among sites sampled within a single water system and by fluctuations in the concentration of *Legionella* spp. in the same site.[440,441] In addition, the risk of illness following exposure to a given source may be influenced by a number of factors other than the presence or concentration of organisms; these include the degree to which contaminated water is aerosolized into respirable droplets, the proximity of the infectious aerosol to potential host, the susceptibility of the host, and the virulence properties of the contaminating strain.[442-444] Thus, data are insufficient to assign a level of risk of disease even on the basis of the number of colony-forming units detected in samples from the hospital environment. By routinely culturing water samples, many hospitals will have to be committed to water-decontamination programs to eradicate *Legionella* spp. Because of this problem, routine monitoring of water from the hospital's potable water system and from aerosol-producing devices is not widely recommended.[445]

The second approach to prevent and control nosocomial legionellosis is by (a) maintaining a high index of suspicion for legionellosis and appropriately using diagnostic tests for legionellosis in patients with nosocomial pneumonia who are at high risk of developing the disease and dying from the infection,[385,446] (b) initiating an investigation for a hospital source of *Legionella* spp. upon identification of one case of definite or two cases of possible nosocomial Legionnaires' disease, and (c) routinely maintaining cooling towers and using only sterile water for filling and terminal rinsing of nebulization devices.

Measures aimed at creating an environment that is not conducive to survival or multiplication of *Legionella* spp. have been advocated and utilized in hospitals where cases of nosocomial legionellosis have been identified; these include routine maintenance of potable water at ≥ 50°C or < 20°C at the tap or chlorination of heated water to achieve 1-2 mg/L free residual chlorine at the tap, especially in areas where immunosuppressed and other high-risk patients are located.[385,429,440,447-450] However, the cost-benefit ratio of such measures in hospitals with no identified cases of legionellosis needs further study.

B. Prevention of Legionnaires' Disease in Hospitals with Identified Cases (Secondary Prevention)

The indications for a full-scale environmental investigation to search for and subsequently decontaminate identified sources of *Legionella* spp. in hospital environments remain to be elucidated, and probably vary from hospital to hospital. In institutions where as few as 1-3 nosocomial cases are identified over a period of up to several months, intensified surveillance for Legionnaires' disease has frequently detected numerous additional cases.[404,423,426,448] This suggests the need for a low threshold for initiating an investigation following the identification of nosocomial, laboratory-confirmed cases of legionellosis. However, when developing a strategy to respond to such an identification, infection-control personnel should consider the level of risk of nosocomial acquisition of, and mortality from, *Legionella* spp. infection at their particular hospital.

An epidemiologic investigation of the source of *Legionella* spp. involves several important steps, including retrospective review of microbiologic and medical records; active surveillance to identify all recent or ongoing cases of legionellosis; identification of potential risk factors (including environmental exposures for infection, such as showering or use of respiratory therapy equipment) by line listing of cases, analysis by time, place, and person, and comparison with appropriate controls; collection of water samples from environmental sources implicated by the epidemiologic investigation and from other potential sources of aerosolized water; and subtype-matching between legionellae isolated from patients and environmental samples.[428,452-454] The latter step can be crucial in supporting epidemiologic evidence of a link between human illness and a specific source.[455]

In hospitals where the heated-water system has been identified as the source of the organism, the system has been decontaminated by pulse (one-time) thermal disinfection or superheating (ie, flushing for at least 5 minutes each distal outlet of the hot-water system with

water at ≥ 65°C) and hyperchlorination (flushing all outlets of the hot-water system with water containing ≥ 10 mg/L free residual chlorine).[450,456-458] Following either of these procedures, most hospitals maintain heated water at ≥ 50°C or < 20°C at the tap or chlorinate heated water to achieve 1-2 mg/L free residual chlorine at the tap.[385,429,440,447-450] Additional measures, such as physical cleaning or replacement of hot-water storage tanks, water-heaters, faucets, and showerheads, may be required because scale and sediment that provide organisms protection from the biocidal effects of heat and chlorine, may accumulate in them.[393,450] Alternative methods for control and eradication of legionellae in water systems, such as treatment of water with ozone, ultraviolet light, or heavy metal ions, have limited the growth of legionellae under laboratory and/or operating conditions.[391,459-463] However, further data are needed regarding the efficacy of these methods before they can be considered standard. In hospitals where the cooling towers are contaminated, measures for decontamination have been previously published.[464]

For highly immunocompromised patients, other preventive measures have been used. At one hospital, immunosuppressed patients were restricted from taking showers, and, for these patients, only sterile water was used for drinking or flushing nasogastric tubes.[430] In another hospital, a combined approach, consisting of continuous heating, particulate filtration, ultraviolet treatment, and monthly pulse hyperchlorination of the water supply of the bone-marrow transplant unit, was used to decrease the incidence of Legionnaires' disease.[459]

In view of the high cost of an environmental investigation and of instituting control measures to eradicate *Legionella* spp. from sources in the hospital[465,466] and the differential risk, based on host factors, for acquiring nosocomial legionellosis and of having severe and fatal infection with the microorganism, the decision to search for and the choice of procedures to eradicate hospital environmental sources of *Legionella* spp. should take into account the type of patient population served by the hospital.

ASPERGILLOSIS

I. Epidemiology

Aspergillus spp. are ubiquitous fungi, commonly occurring in soil, water, and decaying vegetation. *Aspergillus* spp. have been cultured from unfiltered air, ventilation systems, contaminated dust dislodged during hospital renovation and construction, horizontal surfaces, food, and ornamental plants.[467]

A fumigatus and *A flavus* are the most frequently isolated *Aspergillus* spp. in patients with proven aspergillosis.[468] Nosocomial aspergillosis has been recognized increasingly as a cause of severe illness and mortality in highly immunocompromised patients, eg, patients undergoing chemotherapy and/or organ transplantation, including bone-marrow transplantation for hematologic and other malignant neoplasms.[469-473]

The most important nosocomial infection due to *Aspergillus* spp. is pneumonia.[474,495] Hospital outbreaks of pulmonary aspergillosis have occurred mainly in granulocytopenic patients, especially in bone-marrow transplant units.[474-480] Although invasive aspergillosis has been reported in recipients of solid-organ transplants (eg, heart or kidney),[481-485] the incidence of *Aspergillus* spp. infections in these patients has been lower than in recipients of bone-marrow transplants, probably because granulocytopenia is less severe in solid-organ transplant recipients and the use of corticosteroids has decreased with the introduction of cyclosporine.[483,486] In solid-organ transplant recipients, the efficacy of infection control measures, such as provision of protected environments and prophylaxis with antifungal agents, in preventing aspergillosis has not been well evaluated.[483,484,486,489] In one study of heart-transplant recipients, protective isolation of patients alone failed to prevent fungal infections.[490]

The reported attributable mortality from invasive pulmonary aspergillosis has varied, depending on the patient population studied. Rates have been as high as 95% in recipients of allogeneic bone-marrow transplants and patients with aplastic anemia, compared with rates of 13-80% in leukemic patients.[491-493]

II. Pathogenesis

In contrast to most bacterial pneumonias, the primary route of acquiring *Aspergillus* spp. infection is by inhalation of the fungal spores. In severely immunocompromised patients, primary *Aspergillus* spp. pneumonia results from local lung tissue invasion.[468,494,495] Subsequently, the fungus may disseminate via the bloodstream to involve multiple other deep organs.[468,495,496] A role for nasopharyngeal colonization with *Aspergillus* spp., as an intermediate step before invasive pulmonary disease, has been proposed, but remains to be elucidated.[488,497,498] On the other hand, colonization of the lower respiratory tract by *Aspergillus* spp., especially in patients with preexisting lung disease such as chronic obstructive lung disease, cystic fibrosis, or inactive tuberculosis, has predisposed patients to invasive pulmonary and/or disseminated infection.[468,495,499]

III. Diagnosis

Diagnosing pneumonia due to *Aspergillus* spp. is often difficult without performing invasive procedures. Bronchoalveolar lavage has been a useful screening test,[500-502] but lung biopsy is still considered the most reliable technique.[503] Histopathologic demonstration of tissue invasion by fungal hyphae has been required in addition to isolation of *Aspergillus* spp. from respiratory tract secretions because the latter, by itself, may indicate colonization.[504] However, when *Aspergillus* spp. is grown from the sputum of a febrile, granulocytopenic patient with a new pulmonary infiltrate, it is highly likely that the patient has pulmonary aspergillosis.[497,505] Routine blood cultures are remarkably insensitive for detecting *Aspergillus* spp.,[506] and systemic antibody responses in immunocompromised patients are likely to be unreliable indicators of infection.[507-509] Antigen-based serologic assays are now being developed in an attempt to allow for the rapid and specific diagnosis of *Aspergillus* spp. infections; however, their clinical usefulness is presently undefined.[510,511]

IV. Risk Factors and Control Measures

The major risk factor for invasive aspergillosis is severe and prolonged granulocytopenia, both disease- and therapy-induced.[512] Since bone-marrow transplant recipients experience the most severe degree of granulocytopenia, they probably constitute the population at highest risk of developing invasive aspergillosis.[492,513] The tendency of bone-marrow transplant recipients to develop severe granulocytopenia (< 1,000 polymorphonucleaur/μL) is associated with the type of graft they receive. While both autologous and allogeneic bone-marrow transplant recipients are severely granulocy-

topenic for up to 4 weeks after the transplant procedure, allogeneic-transplant recipients may, in addition, develop acute or chronic graft-versus-host disease. The latter may occur up to several months after the procedure, and the disease and/or its therapy (often with high doses of corticosteroids, cyclosporine, and other immunosuppressive agents) may result in severe granulocytopenia. Consequently, in developing strategies to prevent invasive *Aspergillus* spp. infection in bone-marrow-transplant patients, infection control personnel should consider exposures of the patient to the fungus not only during the patient's immediate post-transplantation period but also other exposures (eg, at home or in an ambulatory-care setting) subsequent to the immediate post-transplant period, when the patient (especially allogeneic-transplant recipients) may again manifest severe granulocytopenia. To help address this problem, various studies are now in progress to evaluate newer methods of enhancing host resistance to invasive fungal (and other) infections, and of eliminating or suppressing respiratory fungal colonization of the upper respiratory tract. These methods include, respectively, the use of granulocyte-colony-stimulating factors and intranasal application of amphotericin B, or oral or systemic antifungal drug prophylaxis.[467,514-517] For solid-organ transplant recipients, risk factors for invasive aspergillosis have not been as extensively studied. In one study of liver-transplant recipients, risk factors for invasive infection with *Aspergillus* spp. identified by univariate analysis included preoperative and postoperative receipt of steroids and antimicrobial agents, and prolonged duration of transplant surgery.[518]

The presence of aspergilli in the hospital environment is the major extrinsic risk factor for the occurrence of opportunistic invasive *Aspergillus* spp. infection.[487,519] Environmental disturbances due to construction and/or renovation activities in and around hospitals markedly raise the airborne *Aspergillus* spp. spore counts in such hospitals and have been associated with nosocomial aspergillosis.[476,478,479,520-523] In addition, aspergillosis in high-risk immunosuppressed patients has been associated with other hospital environmental reservoirs, including bird droppings in air ducts supplying high-risk patient areas,[524] and contaminated fireproofing material or damp wood.[478,525]

A single case of nosocomial *Aspergillus* spp. pneumonia is often difficult to link to a specific environmental exposure. However, additional cases may remain undetected without an active search that includes an intensive retrospective review of microbiologic, histopathologic, and postmortem records; notification of clinicians caring for high-risk patients; and establishment of a system for prospective surveillance for additional cases. When additional cases are detected, the likelihood is increased that a hospital environmental source of *Aspergillus* spp. can be identified.[476,478,520-525] Previous investigations have shown the importance of construction activities and/or fungal "contamination" of hospital air-handling systems as major sources for outbreaks.[474,476,478,520-524] New molecular typing techniques, namely karyotyping[526] and DNA endonuclease profiling (now available for *A fumigatus*),[527] may significantly aid in identifying the source of an outbreak.

Outbreaks of invasive aspergillosis reinforce the importance of maintaining an environment as free of *Aspergillus* spp. spores as possible for patients with severe granulocytopenia. To achieve this goal, specialized services in many large hospitals, in particular bone-marrow transplant services, have installed "protected environments" for the care of their high-risk, severely granulocytopenic patients, and increased their vigilance during hospital construction and routine maintenance of hospital air-filtration and ventilation systems, to prevent exposing high-risk patients to bursts of fungal spores.[476,478,520-524,528-533]

While the exact configuration and specifications of the protected environments may vary between hospitals, these patient-care areas are built to minimize fungal spore counts in air by maintaining (a) high-efficiency filtration of incoming air by using central or point-of-use HEPA filters that are 99.97% efficient in filtering 0.3μ-sized particles, (b) directed room airflow—from intake on one side of the room, across the patient, and out through the exhaust on the opposite side of the room, (c) positive room-air pressure relative to the corridor, (d) well-sealed rooms, and (e) high rates of room-air changes (range: 15 to > 400 per hour), although air-change rates at the higher levels may pose problems of patient comfort.[474,529-531,533-535] The oldest and most studied protected environment is a room with laminar airflow, consisting of a bank of HEPA filters along an entire wall through which air is pumped by blowers into the room at a uniform velocity (90±20 feet/minute), forcing the air to move in a laminar, or at least unidirectional, pattern.[536] The air usually exits at the opposite end of the room, and ultra-high air-change rates (100-400 per hour) are achieved.[474,528] The net effects are essentially sterile air in the room, minimal air turbulence, minimal opportunity for microorganism build-up, and a consistently clean environment.[474]

The efficacy of a laminar-airflow system in decreasing or eliminating the risk of nosocomial aspergillosis in high-risk patients has been demonstrated.[474,529,534,535] However, such a system is costly to install and maintain. Less expensive alternative systems with lower air-change rates (10-15 per hour) have been utilized in some centers.[530,531,537] However, studies comparing the efficacy of these alternative systems with laminar-airflow rooms in eliminating *Aspergillus* spp. spores and preventing nosocomial aspergillosis are limited. One institution employing cross-flow ventilation, point-of-use high-efficiency filters, and 15 air changes per hour reported that cases of nosocomial aspergillosis in patients housed in these rooms have occurred, albeit at a low rate (3.4%).[531,537] The infections, however, were due to *A flavus*—a species that was never cultured from the room air, suggesting that the patients were probably exposed to fungal spores when they were allowed outside their rooms.[531]

Copper-8-quinolinolate has been used on environmental surfaces contaminated with *Aspergillus* spp. to control a reported outbreak,[538] and incorporated in fireproofing material of a newly constructed hospital[531] to help decrease the environmental spore burden, but its general applicability is yet to be established.

VIRAL PNEUMONIAS

Viruses can be an important and often unappreciated cause of nosocomial pneumonia.[539-541] In one prospective study of endemic nosocomial infections, approximately 20% of patients with pneumonia had viral infections.[540] Although early diagnosis and treatment of viral infections have become possible in recent years,[542-545] many hospitalized patients remain at high risk for developing severe and sometimes fatal viral infections.[539,546-553] Based on these data and on

well-documented outbreaks with nosocomial viral transmission,[554-557] measures to prevent viral transmission should be instituted.

Nosocomial respiratory viral infections (1) usually follow community outbreaks that occur during a particular period every year,[556,558-561] (2) confer only short-term immunity,[562] (3) affect healthy and ill persons,[548,549,555,563-565] and (4) have exogenous sources. A number of viruses, including adenoviruses, influenza virus, measles virus, parainfluenza viruses, respiratory syncytial virus (RSV), rhinoviruses, and varicella-zoster virus can cause nosocomial pneumonia;[549,556,557,566-572,574] however, adenoviruses, influenza viruses, parainfluenza viruses, and RSV have been reported to account for most (70%) of nosocomial pneumonias due to viruses.[573]

Because influenza and RSV infections substantially contribute to patient morbidity and mortality associated with viral pneumonia and have been well studied epidemiologically, this section focuses on the principles and approaches to control these infections. Prevention of nosocomial infections due to other viral pathogens are addressed in another document.[224]

RSV INFECTION

I. Epidemiology

RSV infection is most common during infancy and early childhood, but may also occur in adults.[563,566,575,576] Infection usually causes mild or moderately severe upper respiratory illness. However, life-threatening pneumonia or bronchiolitis has been reported in children with chronic cardiac and pulmonary disease, immunocompromised patients, and the elderly.[548,550,565,566,577,578]

Recent surveillance of 10 U.S. hospital laboratories performing cultures for RSV suggests that community outbreaks occur yearly between December and March, last from 3-5 months, and are associated with increased hospitalization and deaths among infants and young children.[579] During community outbreaks of RSV, children admitted to the hospital with respiratory symptoms often serve as reservoirs for RSV.[554,556]

II. Diagnosis

The clinical characteristics of RSV infection, especially in neonates, are often indistinguishable from those of other viral respiratory tract infections.[566,567] Culture of RSV from respiratory secretions remains the "gold standard" for diagnosis. Although rapid antigen-detection kits utilizing direct immunofluorescence or enzyme-linked immunosorbent assay are available and can provide results within hours, the benefit of using these tests to identify infected patients depends on the sensitivity and specificity of the test. The reported sensitivity and specificity of RSV enzyme immunoassays vary between 80% and 95%, and may even be lower in actual practice.[580-583] In general, once laboratory-confirmed cases of RSV infection are identified in a hospital, a presumptive diagnosis of RSV infection in subsequent cases with manifestations suggestive of RSV infection may be acceptable for infection control purposes.

III. Modes of Transmission

RSV is present in large numbers in the respiratory secretions of symptomatic persons infected with the virus and can be transmitted directly via large droplets during close contact with such persons, or indirectly via RSV-contaminated hands or fomites.[554,584,585] The portal of entry is usually the conjunctiva or the nasal mucosa.[586] Inoculation by RSV-contaminated hands is the usual way of depositing the virus onto the eyes or nose.[554,584-586] Hands can become contaminated through handling of infected persons' respiratory secretions or contaminated fomites.[584,585]

In nosocomial RSV outbreaks in which the viral isolates were typed, more than one strain of RSV has often been identified,[555,564,587] suggesting multiple sources of the virus. Potential sources include patients, hospital staff, and visitors. Because infected infants shed large amounts of virus in their respiratory secretions and easily contaminate their immediate surroundings, they are a major reservoir for RSV.[588] Hospital staff may become infected after exposure in the community[589] or in the hospital and, in turn, infect patients, other health-care workers, or hospital visitors.[567,590]

IV. Control Measures

Various combinations of control measures ranging from the simple to the complex have been effective, to some degree or other, in preventing and controlling nosocomial RSV infection.[226,590-597] Successful programs have had two elements in common: implementation of contact isolation precautions, and compliance with these precautions by health-care personnel. In theory, strict handwashing should prevent most nosocomial RSV infections. However, health-care workers' handwashing practices have always been poor.[221,222] Thus, other preventive measures are usually relied upon to prevent RSV infection.

The basic precautions that have been associated with decreased incidence of nosocomial RSV infections are gloving and gowning.[226] Gloving has helped decrease transmission probably because gloves remind patient-care personnel to comply with handwashing and other precautions, and deter persons from touching their eyes or noses. The benefits from gloving, however, are offset if gloves are not changed between patients or after contact with contaminated fomites, and if hands are not adequately washed after glove removal.[229] Gowning, in combination with gloving, during contact with RSV-infected infants or their immediate environment has been used successfully to prevent infection.[226] In addition, the use of eye-nose goggles rather than masks has protected health-care workers from infection; however, eye-nose goggles are not widely available and are inconvenient to wear.[594,598]

Additional measures may be indicated to control ongoing nosocomial transmission of RSV or to prevent transmission to patients at high risk for serious complications of infections, such as those with compromised cardiac, pulmonary, or immune systems. The following additional control measures have been used in various combinations: (1) use of private rooms for infected patients OR cohorting of infected patients, with or without pre-admission screening by rapid laboratory diagnostic tests; (2) cohorting of personnel; (3) exclusion of health-care workers who have symptoms of upper respiratory tract infection from the care of uninfected patients at high risk of severe or fatal RSV infection, eg, infants; (4) limiting visitors; and (5) postponing admission of patients at high risk of complications from RSV infection.[224,591,593,595,597] Although the exact role of each of these measures has not been fully elucidated, their use for control of outbreaks seems prudent.

INFLUENZA

I. Epidemiology

Pneumonia in patients with influenza

may be due to the influenza virus itself, secondary bacterial infection, or a combination of both.[599-601] Influenza-associated pneumonia can occur in any person, but is more common in the very young or old and in persons in any age group with immunosuppression or certain chronic medical conditions such as severe underlying heart or lung disease.[576,602-604]

Influenza typically occurs annually in the winter between December and April; peak activity in a community usually lasts from 6 to 8 weeks during this period.[605,606] During influenza epidemics in the community, nosocomial outbreaks can occur and are often characterized by abrupt onset and rapid transmission.[607-609] Most reported institutional outbreaks of influenza have occurred in nursing homes; however, hospital outbreaks have been reported on pediatric and chronic-care wards, as well as on medical and neonatal intensive care units.[557,610-613]

Influenza is believed to be spread from person to person by direct deposition of virus-laden large droplets onto the mucosal surfaces of the upper respiratory tract of an individual during close contact with an infected person, as well as by droplet nuclei or small-particle aerosols.[614-617] The extent to which transmission may occur by virus-contaminated hands or fomites is unknown; however, it is not the primary mode of spread.[618]

The most important reservoirs of influenza virus are infected persons, and the period of greatest communicability is during the first 3 days of illness; however, the virus can be shed before onset of symptoms, and up to 7 or more days after illness onset.[351,557,605]

II. Diagnosis

Influenza is clinically indistinguishable from other febrile respiratory illnesses, but during outbreaks with laboratory-confirmed cases, a presumptive diagnosis of the infection can be made in cases with similar manifestations.[619] In the past, diagnosis of influenza was made by virus isolation from nasopharyngeal secretions or by serologic conversion, but recently developed rapid diagnostic tests that are similar to culture in sensitivity and specificity allow early diagnosis and treatment of cases and provide a basis for prompt initiation of antiviral prophylaxis as part of outbreak control.[620-625]

III. Prevention and Control of Influenza

Vaccination of persons at high risk for complications of influenza is currently the most effective measure for reducing the impact of influenza, and should be done before the influenza season each year. High-risk persons include those ≥ 65 years of age; those in long-term-care units; those with chronic disorders of the pulmonary or cardiovascular systems; those with diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression; and children 6 months-18 years of age who are receiving long-term aspirin therapy.[612,626-628] Patients with musculo-skeletal disorders that impede adequate respiration may also be at high risk of developing complications of influenza. When high vaccination rates are achieved in closed or semi-closed settings, the risk of outbreaks is reduced because of induction of herd immunity.[629,630]

When an institutional outbreak is caused by influenza type A, antiviral agents may be used both for treatment of ill persons and as prophylaxis for others.[642] Two related antiviral agents, amantadine hydrochloride and rimantadine hydrochloride, are effective against influenza type A, but not influenza type B, virus.[544,632-634] These agents can be used to prevent influenza type A (1) as short-term prophylaxis after late vaccination of high-risk persons; (2) as prophylaxis for persons for whom vaccination is contraindicated; (3) as prophylaxis for immunocompromised persons who may not produce protective levels of antibody in response to vaccination; (4) as prophylaxis for unvaccinated health-care workers who provide care to high-risk patients, either for the duration of influenza activity in the community or until immunity develops after vaccination; and (5) when vaccine strains do not closely match the epidemic virus strain.[642]

Amantadine has been available in the United States for many years; rimantadine has been approved for use since 1993. Both drugs protect against all naturally-occurring strains of type A influenza virus; thus, antigenic changes in the virus that may reduce vaccine efficacy do not alter the effectiveness of amantadine or rimantadine. Both drugs are 70-90% effective in preventing illness if taken before exposure to influenza A virus.[632,635] In addition, they can reduce the severity and duration of illness due to influenza type A when administered within 24-48 hours after onset of symptoms.[636,637] These drugs can limit nosocomial spread of influenza type A if they are administered to all or most patients when influenza type A illnesses begin in a facility.[610,638,639]

Compared to rimantadine, amantadine has been associated with a higher incidence of adverse central nervous system (CNS) reactions such as mild and transitory nervousness, insomnia, impaired concentration, mood changes, and light-headedness. These symptoms have been reported in 5%-10% of healthy young adults receiving 200 mg of amantadine per day.[544,632] In the elderly, CNS side effects may be more severe; in addition, dizziness and ataxia are more common in this age group.[640,641] Dose reductions of both amantadine and rimantadine are recommended for certain patient groups, such as persons ≥ 65 years of age and/or those who have renal insufficiency. The drug package insert for amantadine or rimantadine contains important information regarding administration of either drug. Guidelines for the use of these drugs and considerations for the selection of amantadine or rimantadine have been developed by the Advisory Committee for Immunization Practices.[642]

Emergence of amantadine- and rimantadine-resistant strains of influenza A virus has been observed in persons who have received these drugs for treatment of the infection.[643,644] Because of the potential risk of transmission of resistant viral strains to contacts of persons receiving amantadine or rimantadine for treatment,[644,645] to the extent possible, infected persons taking either drug should avoid contact with others during treatment and for 2 days after discontinuing treatment.[645,646] This is particularly important if the contacts are uninfected high-risk persons.[645,647]

Vaccination of high-risk patients and of hospital personnel before the influenza season is the primary focus of efforts to prevent and control nosocomial influenza.[628,631,648] The decision to use amantadine or rimantadine as an adjunct to vaccination in the prevention and control of nosocomial influenza is based in part on results of virologic and epidemiologic surveillance in the hospital and the community. When outbreaks of influenza type A occur in a hospital, and antiviral prophylaxis of high-risk persons and/or treatment of cases is undertaken, administration of amantadine or rimantadine

is begun as early in the outbreak as possible to reduce transmission.[610,631,642,647]

Measures other than vaccination and chemoprophylaxis have been recommended for control of nosocomial influenza outbreaks. Because influenza can be transmitted during contact with an infected person, contact isolation precautions, placing a patient symptomatic with influenza in a private room, cohorting of patients with influenza-like illness, and masking upon entering a room with persons with suspected or proven influenza have been recommended.[224] Handwashing, gloving, and gowning by health-care workers during the patient's symptomatic period have also been recommended, but the exact role of these measures in preventing influenza transmission remains to be elucidated.[224,609,649] Although influenza can be transmitted via the airborne route, the efficacy of placing infected persons in rooms with negative pressure in relation to their immediate environment has not been assessed. In addition, this measure may be impractical during institutional outbreaks that occur in the midst of a community epidemic of influenza because many newly admitted patients and health-care workers may be infected with the virus; thus, the hospital would face the logistical problem of accommodating all ill persons in rooms with special ventilation. Although controlled studies are not available to measure their effectiveness, the following additional measures have been recommended for consideration, particularly during severe outbreaks: (1) curtailment or elimination of elective admissions, both medical and surgical; (2) restriction of cardiovascular and pulmonary surgery; (3) restriction of hospital visitors, especially those with acute respiratory illnesses; and (4) work restriction for health-care workers with acute respiratory illness.[649]

PART II. RECOMMENDATIONS FOR PREVENTION OF NOSOCOMIAL PNEUMONIA

The Hospital Infection Control Practices Advisory Committee

INTRODUCTION

The recommendations are presented according to the etiology of the infection, in the following order: bacterial pneumonia, including Legionnaires' disease; fungal pneumonia (aspergillosis); and virus-associated pneumonia (respiratory syncytial virus [RSV] and influenza infections). Each topic is subdivided according to the following general approaches for nosocomial infection control, as applicable to the infection:

1. staff education and infection surveillance;
2. interruption of transmission of microorganisms by eradicating infecting microorganisms from their epidemiologically important reservoirs, and/or preventing person-to-person transmission; and
3. modifying host risk for infection.

As in previous CDC guidelines, each recommendation is categorized on the basis of existing scientific evidence, theoretical rationale, applicability, and economic impact.[224,225,650-654] However, the previous CDC system of categorizing recommendations has been modified as follows:

CATEGORY IA. Strongly recommended for all hospitals and strongly supported by well-designed experimental or epidemiologic studies.

CATEGORY IB. Strongly recommended for all hospitals and viewed as effective by experts in the field and a consensus of HICPAC based on strong rationale and suggestive evidence, even though definitive scientific studies may not have been done.

CATEGORY II. Suggested for implementation in many hospitals. Recommendations may be supported by suggestive clinical or epidemiologic studies, a strong theoretical rationale, or definitive studies applicable to some but not all hospitals.

NO RECOMMENDATION; UNRESOLVED ISSUE. Practices for which insufficient evidence or consensus regarding efficacy exists.

BACTERIAL PNEUMONIA

I. Staff Education and Infection Surveillance

A. Staff Education

Educate health-care workers regarding nosocomial bacterial pneumonias and infection control procedures to prevent their occurrence.[655-661] ***CATEGORY IA***

B. Surveillance

1. Conduct surveillance for bacterial pneumonia in ICU patients at high risk for nosocomial bacterial pneumonia (eg, patients with mechanically assisted ventilation, selected postoperative patients) to determine trends and identify potential problems.[6,34,35,62,63,662-664] Include data regarding the causative microorganisms and their antimicrobial susceptibility patterns.[2,3] Express data as rates (eg, number of infected patients or infections per 100 ICU days or per 1,000 ventilator-days) to facilitate intra-hospital comparisons and determine trends.[66,665-667] ***CATEGORY IA***

2. Do not routinely perform surveillance cultures of patients or of equipment or devices used for respiratory therapy, pulmonary-function testing, or delivery of inhalation anesthesia.[65,668,669] ***CATEGORY IA***

II. Interruption of Transmission of Microorganisms

A. Sterilization or Disinfection and Maintenance of Equipment and Devices

1. General Measures

a. Thoroughly clean all equipment and devices to be sterilized or disinfected.[266,267,670] ***CATEGORY IA***

b. Sterilize or use high-level disinfection for semicritical equipment or devices, ie, items that come into direct or indirect contact with mucous membranes of the lower respiratory tract (See examples, Appendix A). High-level disinfection can be achieved either by wet-heat pasteurization at 76°C for 30 minutes or by using liquid chemical disinfectants approved as sterilants/disinfectants by the Environmental Protection Agency and cleared for marketing for use on medical instruments by the Office of Device Evaluation, Center for Devices and Radiologic Health, Food and Drug Administration.[260,262,264-267,671] Follow disinfection with appropriate rinsing, drying, and packaging, taking care not to contaminate the items in the process. ***CATEGORY IB***

c. (1) Use sterile (not distilled, nonsterile) water for rinsing reusable semicritical equipment and devices used on the respiratory tract after they have been chemically disinfected.[241,249,250,258,269] ***CATEGORY IB***

(2) *No recommendation* for using tap water (as an alternative to sterile water) to rinse reusable semicritical equipment and devices used on the respiratory tract after they have been subjected to high-level disinfection, whether or not rinsing is followed by drying with or without the use of alcohol.[241,249,250,258,269,273,277] ***UNRESOLVED ISSUE***

d. Do not reprocess an equipment or device that is manufactured for single use only,

unless data show that reprocessing the equipment or device poses no threat to the patient, is cost-effective, and does not change the structural integrity or function of the equipment or device.[672,673] ***CATEGORY IB***

2. Mechanical Ventilators, Breathing Circuits, Humidifiers, and Heat-Moisture Exchangers

a. Mechanical Ventilators

Do not routinely sterilize or disinfect the internal machinery of mechanical ventilators.[126,128,674] ***CATEGORY IA***

b. Ventilator Circuits with Humidifiers

(1) Do not routinely change more frequently than every 48 hours the breathing circuit, including tubing and exhalation valve, and the attached bubbling or wick humidifier of a ventilator that is in use on an individual patient.[34,283,288] ***CATEGORY IA***

(2) *No recommendation* for the maximum length of time after which the breathing circuit and the attached bubbling or wick humidifier of a ventilator in use on a patient should be changed.[289] ***UNRESOLVED ISSUE***

(3) Sterilize reusable breathing circuits and bubbling or wick humidifiers, or subject them to high-level disinfection between their uses on different patients.[259,260,262,264,267] ***CATEGORY IB***

(4) Periodically drain and discard any condensate that collects in the tubing of a mechanical ventilator, taking precautions not to allow condensate to drain toward the patient. Wash hands after performing the procedure or handling the fluid.[215,282,296] ***CATEGORY IB***

(5) *No recommendation* for placing a filter or trap at the distal end of the expiratory-phase tubing of the breathing circuit to collect condensate.[247,282] ***UNRESOLVED ISSUE***

(6) Do not place bacterial filters between the humidifier reservoir and the inspiratory-phase tubing of the breathing circuit of a mechanical ventilator. ***CATEGORY IB***

(7) Humidifier fluids

(a) Use sterile water to fill bubbling humidifiers.[132,241,249,250,296] ***CATEGORY II***

(b) Use sterile, distilled, or tap water to fill wick humidifiers.[249,250,296] ***CATEGORY II***

(c) *No recommendation* for the preferential use of a closed, continuous-feed humidification system. ***UNRESOLVED ISSUE***

c. Ventilator Breathing Circuits with Hygroscopic Condenser-Humidifiers or Heat-Moisture Exchangers

(1) *No recommendation* for the preferential use of hygroscopic condenser-humidifier or heat-moisture exchanger rather than a heated humidifier to prevent nosocomial pneumonia.[298-302] ***UNRESOLVED ISSUE***

(2) Change the hygroscopic condenser-humidifier or heat-moisture exchanger according to manufacturer's recommendation and/or when evidence of gross contamination or mechanical dysfunction of the device is present.[298] ***CATEGORY IB***

(3) Do not routinely change the breathing circuit attached to a hygroscopic condenser-humidifier or heat-moisture exchanger while it is in use on a patient.[298,301] ***CATEGORY IB***

3. Wall Humidifiers

a. Follow manufacturers' instructions for use and maintenance of wall oxygen humidifiers unless data show that the modification in their use or maintenance poses no threat to the patient and is cost-effective.[675-679] ***CATEGORY IB***

b. Between patients, change the tubing, including any nasal prongs or mask, used to deliver oxygen from a wall outlet. ***CATEGORY IB***

4. Small-Volume Medication Nebulizers: "In-line" and Hand-Held Nebulizers

a. (1) Between treatments on the same patient, disinfect, rinse with sterile water, or air-dry small-volume medication nebulizers.[242,258] ***CATEGORY IB***

(2) *No recommendation* for using tap water as an alternative to sterile water to rinse reusable small-volume medication nebulizers between treatments on the same patient.[242,258,273] ***UNRESOLVED ISSUE***

b. Between patients, replace nebulizers with those that have undergone sterilization or high-level disinfection.[126,128,129,269,680] ***CATEGORY IB***

c. Use only sterile fluids for nebulization, and dispense these fluids aseptically.[238, 241,249,250,258,269,304] ***CATEGORY IA***

d. If multidose medication vials are used, handle, dispense, and store them according to manufacturers' instructions.[238,304,680-682] ***CATEGORY IB***

5. Large-Volume Nebulizers and Mist Tents

a. Do not use large-volume room-air humidifiers that create aerosols (eg, by venturi principle, ultrasound, or spinning disk) and thus are really nebulizers, unless they can be sterilized or subjected to high-level disinfection at least daily and filled only with sterile water.[239-241,252,303,683] ***CATEGORY IA***

b. Sterilize large-volume nebulizers that are used for inhalation therapy, eg, for tracheostomized patients, or subject them to high-level disinfection between patients and after every 24 hours of use on the same patient.[126,128,129] ***CATEGORY IB***

c. (1) Use mist-tent nebulizers and reservoirs that have undergone sterilization or high-level disinfection and replace them between patients.[684] ***CATEGORY IB***

(2) *No recommendation* regarding the frequency of changing mist-tent nebulizers and reservoirs while in use on one patient. ***UNRESOLVED ISSUE***

6. Other Devices Used in Association with Respiratory Therapy

a. Between patients, sterilize or subject to high-level disinfection portable respirometers, oxygen sensors, and other respiratory devices used on multiple patients.[233,245] ***CATEGORY IB***

b. (1) Between patients, sterilize or subject to high-level disinfection reusable hand-powered resuscitation bags (for example, Ambu bags).[255,311-313] ***CATEGORY IA***

(2) *No recommendation* regarding the frequency of changing hydrophobic filters placed on the connection port of resuscitation bags. ***UNRESOLVED ISSUE***

7. Anesthesia Machines and Breathing Systems or Patient Circuits

a. Do not routinely sterilize or disinfect the internal machinery of anesthesia equipment.[316] ***CATEGORY IA***

b. Clean and then sterilize or subject to high-level liquid chemical disinfection or pasteurization reusable components of the breathing system or patient circuit (eg, tracheal tube or face mask; inspiratory and expiratory breathing tubing; Y-piece; reservoir bag; humidifier and tubing) between uses on different patients, by following the device manufacturer's instructions for their reprocessing.[260,264,267,317,685] ***CATEGORY IB***

c. *No recommendation* for the frequency of routinely cleaning and disinfecting unidirectional valves and carbon dioxide absorber chambers.[317-319] ***UNRESOLVED ISSUE***

d. Follow published guidelines and/or manufacturers' instructions regarding in-use maintenance, cleaning, and disinfection or sterilization of other components or attachments of the breathing system or patient circuit of anesthesia equipment.[317,318] ***CATEGORY IB***

e. Periodically drain and discard any condensate that collects in the tubing of a breathing circuit, taking precautions not to allow condensate to drain toward the patient. After performing the procedure or handling the fluid, wash hands with soap and water or with a waterless handwashing preparation.[218,219,686,687] ***CATEGORY IB***

f. *No recommendation* for placing a bacterial filter in the breathing system or patient circuit of anesthesia equipment.[1,317,318,321-326,688] ***UNRESOLVED ISSUE***

8. Pulmonary-Function Testing Equipment

a. Do not routinely sterilize or disinfect the internal machinery of pulmonary-function testing machines between uses on different patients.[327,328] ***CATEGORY II***

b. Sterilize or subject to high-level liquid chemical disinfection or pasteurization reusable mouthpieces and tubings or connectors between uses on different patients, OR follow device manufacturer's instructions for their reprocessing.[260,261,263-267] ***CATEGORY IB***

B. Interruption of Person-to-Person Transmission of Bacteria

1. Handwashing. Wash hands after contact with mucous membranes, respiratory secretions, or objects contaminated with respiratory secretions, whether or not gloves are worn. Wash hands before and after contact with a patient who has an endotracheal or tracheostomy tube in place, and before and after contact with any respiratory device that is used on the patient, whether or not gloves are worn.[210,212,218,219,231,689,690] ***CATEGORY IA***

2. Barrier Precautions

a. Wear gloves for handling respiratory secretions or objects contaminated with respiratory secretions of any patient.[226,227] ***CATEGORY IA***

b. Change gloves and wash hands between patients; after handling respiratory secretions or objects contaminated with secretions from one patient and before contact with another patient, object, or environmental surface; and between contacts with a contaminated body site and respiratory tract of, or respiratory device on, the same patient.[226,228-230] ***CATEGORY IA***

c. Wear a gown when soiling with respiratory secretions from a patient is anticipated, and change the gown after such contact and before providing care to another patient.[226] ***CATEGORY IB***

3. Care of Patients with Tracheostomy

a. Perform tracheostomy under sterile conditions. ***CATEGORY IB***

b. When changing a tracheostomy tube, use aseptic technique and replace the tube with one that has undergone sterilization or high-level disinfection. ***CATEGORY IB***

4. Suctioning of Respiratory Tract Secretions

a. *No recommendation* for wearing sterile rather than clean gloves when suctioning a patient's respiratory secretions. ***UNRESOLVED ISSUE***

b. If the open suction system is employed, use a sterile single-use catheter. ***CATEGORY II***

c. Use only sterile fluid to remove secretions from the suction catheter if the catheter is to be used for re-entry into the patient's lower respiratory tract.[691] ***CATEGORY IB***

d. *No recommendation* for preferential use of the multi-use closed-system suction catheter or the single-use open-system catheter for prevention of pneumonia.[305-308,310] ***UNRESOLVED ISSUE***

e. Change suction collection tubing (up to the canister) between patients. ***CATEGORY IB***

f. Change suction collection canisters between uses on different patients except when used in short-term care units. ***CATEGORY IB***

III. Modifying Host Risk for Infection

A. Precautions for Prevention of Endogenous Pneumonia

Discontinue enteral-tube feeding and remove devices such as endotracheal, tracheostomy, and/or enteral (ie, oro- or nasogastric, or jejunal) tubes from patients as soon as the clinical indications for these are resolved.[6,34,35,85-87,117,183,185,186,202,692] ***CATEGORY IB***

1. Prevention of Aspiration Associated with Enteral Feeding

a. If there is no contraindication to the maneuver, elevate at an angle of 30–45° the head of the bed of a patient at high risk of aspiration pneumonia, eg, a person receiving mechanically assisted ventilation and/or has an enteral tube in place.[74,185] ***CATEGORY IB***

b. Routinely verify appropriate placement of the feeding tube.[693-695] ***CATEGORY IB***

c. Routinely assess the patient's intestinal motility (eg, by auscultating for bowel sounds and measuring residual gastric volume or abdominal girth) and adjust the rate and volume of enteral feeding to avoid regurgitation.[692] ***CATEGORY IB***

d. *No recommendation* for the preferential use of small-bore tubes for enteral feeding.[694] ***UNRESOLVED ISSUE***

e. *No recommendation* for administering enteral feeding continuously or intermittently.[70,193,198] ***UNRESOLVED ISSUE***

f. *No recommendation* for preferentially placing the feeding tubes, eg, jejunal tubes, distal to the pylorus.[199,200] ***UNRESOLVED ISSUE***

2. Prevention of Aspiration Associated with Endotracheal Intubation

a. *No recommendation* for using orotracheal rather than nasotracheal tube to prevent nosocomial pneumonia.[699] ***UNRESOLVED ISSUE***

b. *No recommendation* for routinely using an endotracheal tube with a dorsal lumen above the endotracheal cuff to allow drainage (by suctioning) of tracheal secretions that accumulate in the patient's subglottic area.[206] ***UNRESOLVED ISSUE***

c. Before deflating the cuff of an endotracheal tube in preparation for tube removal, or before moving the tube, ensure that secretions are cleared from above the tube cuff. ***CATEGORY IB***

3. Prevention of Gastric Colonization

a. If stress-bleeding prophylaxis is needed for a patient with mechanically assisted ventilation, use an agent that does not raise the patient's gastric pH.[22,34,112,118,122,147-154] ***CATEGORY II***

b. *No recommendation* for selective decontamination of a critically ill, mechanically ventilated, or ICU patient's digestive tract with oral and/or intravenous antimicrobials to prevent gram-negative bacillary (or *Candida* spp.) pneumonia.[155-180] ***UNRESOLVED ISSUE***

c. *No recommendation* for routine acidification of gastric feedings to prevent nosocomial pneumonia.[181] ***UNRESOLVED ISSUE***

B. Prevention of Postoperative Pneumonia

1. Instruct preoperative patients, especially those at high risk of developing pneumonia, regarding frequent coughing, taking deep breaths, and ambulating as soon as medically indicated in the postoperative period.[346,348] High-risk patients include those who will receive anesthesia, especially those who will have an abdominal, thoracic, head, or neck operation, or who have substantial pulmonary dysfunction, such as patients with chronic obstructive lung disease, a musculoskeletal abnormality of the chest, or abnormal pulmonary function tests.[331-334, 337,338] ***CATEGORY IB***

2. Encourage postoperative patients to cough frequently, take deep breaths, move about the bed, and ambulate unless it is medically contraindicated.[345,346,348] ***CATEGORY IB***

3. Control pain that interferes with coughing and deep breathing during the immediate

postoperative period by using systemic analgesia.[352,701] including patient-controlled analgesia,[353-355] with as little cough-suppressant effect as possible; appropriate support for abdominal wounds, such as tightly placing a pillow across the abdomen; or regional (eg, epidural) analgesia.[356-358] ***CATEGORY IB***

4. Use an incentive spirometer or intermittent positive pressure breathing on patients at high risk of developing postoperative pneumonia.[339,342,343,346,348,349] (See III-B-1 above for definition of high-risk patients.) ***CATEGORY II***

C. Other Prophylactic Procedures for Pneumonia

1. Vaccination of Patients. Vaccinate patients at high risk for complications of pneumococcal infections with pneumococcal polysaccharide vaccine. High-risk patients include persons ≥ 65 years old; adults with chronic cardiovascular or pulmonary disease, diabetes mellitus, alcoholism, cirrhosis, or cerebrospinal fluid leaks; and children and adults with immunosuppression, functional or anatomic asplenia, or HIV infection.[362-364] ***CATEGORY IA***

2. Antimicrobial Prophylaxis. Do not routinely administer systemic antimicrobial agents to prevent nosocomial pneumonia.[74,91,201,366-370,702] ***CATEGORY IA***

3. Use of Rotating "Kinetic" Beds or Continuous Lateral Rotational Therapy. No recommendation for the routine use of "kinetic" beds or continuous lateral rotational therapy (ie, placing patients on beds that turn on their longitudinal axes intermittently or continuously) for prevention of nosocomial pneumonia in patients in the ICU, critically ill patients, or patients immobilized by illness and/or trauma.[372-377,703] ***UNRESOLVED ISSUE***

PREVENTION AND CONTROL OF LEGIONNAIRES' DISEASE

I. Staff Education and Infection Surveillance

A. Staff Education

Educate (1) physicians to heighten their suspicion for cases of nosocomial Legionnaires' disease and to use appropriate methods for its diagnosis, and (2) patient-care, infection-control, and engineering personnel about measures to control nosocomial legionellosis.[659-661] ***CATEGORY IA***

B. Surveillance

1. Establish mechanism(s) to provide clinicians with appropriate laboratory tests for the diagnosis of Legionnaires' disease.[386,414,415,419,704] ***CATEGORY IA***

2. Maintain a high index of suspicion for the diagnosis of nosocomial Legionnaires' disease, especially in patients who are at high-risk of acquiring the disease (patients who are immunosuppressed, including organ-transplant patients, patients with AIDS, and patients receiving systemic steroids; are ≥ 65 years of age; or have chronic underlying disease such as diabetes mellitus, congestive heart failure, and chronic obstructive lung disease).[385,386,400,402-406,412] Refer to the accompanying background document for definition of nosocomial legionellosis. ***CATEGORY II***

3. *No recommendation* for routinely culturing water systems for Legionella spp.[271,385,429,433,435,436,438-440,456,705] ***UNRESOLVED ISSUE***

II. Interruption of Transmission of Legionella Spp.

A. Primary Prevention (Preventing Nosocomial Legionnaires' Disease When No Cases Have Been Documented)

1. Nebulization and Other Devices

a. (1) Use sterile (not distilled, nonsterile) water for rinsing nebulization devices and other semicritical respiratory-care equipment after they have been cleaned and/or disinfected.[258,271,706] ***CATEGORY IB***

(2) *No recommendation* for using tap water as an alternative to sterile water to rinse reusable semicritical equipment and devices used on the respiratory tract, after they have been subjected to high-level disinfection, whether or not rinsing is followed by drying with or without the use of alcohol. ***UNRESOLVED ISSUE***

b. Use only sterile (not distilled, nonsterile) water to fill reservoirs of devices used for nebulization.[241,252,258,271,706] ***CATEGORY IA***

c. Do not use large-volume room-air humidifiers that create aerosols (eg, by venturi principle, ultrasound, or spinning disk) and thus are really nebulizers, unless they can be sterilized or subjected to high-level disinfection daily and filled only with sterile water.[252,706] ***CATEGORY IA***

2. Cooling Towers

a. When a new hospital building is constructed, place cooling tower(s) in such a way that the tower drift is directed away from the hospital's air-intake system, and design the cooling towers such that the volume of aerosol drift is minimized.[422,707] ***CATEGORY IB***

b. For operational cooling towers, install drift eliminators, regularly use an effective biocide, maintain the tower according to manufacturers' recommendations, and keep adequate maintenance records. (See Appendix D.)[422,464,708] ***CATEGORY IB***

3. Water-Distribution System

a. *No recommendation* for routinely maintaining potable water at the outlet at ≥ 50°C or < 20°C, or chlorinating heated water to achieve 1-2 mg/L free residual chlorine at the tap.[385,429,440,447-450] ***UNRESOLVED ISSUE***

b. *No recommendation* for treatment of water with ozone, ultraviolet light, or heavy-metal ions.[391,460-463,466] ***UNRESOLVED ISSUE***

B. Secondary Prevention (Response to Identification of Laboratory-Confirmed Nosocomial Legionellosis)

When a single case of laboratory-confirmed, *definite* nosocomial Legionnaires' disease is identified, OR if two or more cases of laboratory-confirmed, *possible* nosocomial Legionnaires' disease occur within 6 months of each other (refer to background document for definition of definite and possible nosocomial Legionnaires' disease.):

1. Contact the local or state health department or the CDC if the disease is reportable in the state or if assistance is needed. ***CATEGORY IB***

2. If a case is identified in a severely immunocompromised patient such as an organ-transplant recipient, OR if the hospital houses severely immunocompromised patients, conduct a combined epidemiologic and environmental investigation (as outlined from II-B-3-b-1 through II-B-5, below) to determine the source(s) of *Legionella* spp. ***CATEGORY IB***

3. If the hospital does not house severely immunocompromised patients, conduct an epidemiologic investigation via a retrospective review of microbiologic, serologic, and postmortem data to identify previous cases, and begin an intensive prospective surveillance for additional cases of nosocomial Legionnaires' disease. ***CATEGORY IB***

a. If there is no evidence of continued nosocomial transmission, continue the intensive prospective surveillance (as in II-B-3, above) for at least 2 months after surveillance was begun. ***CATEGORY II***

b. If there is evidence of continued transmission:

(1) Conduct an environmental investigation to determine the source(s) of *Legionella* spp. by collecting water samples from potential sources of aerosolized water, following the methods described in Appendix C and saving and subtyping isolates of *Legionella* spp. obtained from patients and environment.[241,258,422-428,452,454] ***CATEGORY IB***

(2) If a source is not identified, continue surveillance for new cases for at least 2 months, and, depending on the scope of the outbreak, decide on either deferring decontamination pending identification of the source(s) of *Legionella* spp., or proceeding with decontamination of the hospital's water distribution system, with special attention to the specific hospital areas involved in the outbreak. ***CATEGORY II***

(3) If a source of infection is identified by epidemiologic and environmental investigation, promptly decontaminate it.[466] ***CATEGORY IB***

(a) If the heated-water system is implicated:

i. Decontaminate the heated-water system either by superheating (flushing for at least 5 minutes each distal outlet of the system with water at ≥ 65°C), OR by hyperchlorination (flushing for at least 5 minutes all outlets of the system with water containing ≥ 10 mg/L free residual chlorine).[450,452,456,457] Post warning signs at each outlet being flushed to prevent scald injury to patients, staff, or visitors. ***CATEGORY IB***

ii. Depending on local and state regulations regarding potable water temperature in public buildings,[458] maintain potable water at the outlet at ≥ 50°C or < 20°C, or chlorinate heated water to achieve 1-2 mg/L free residual chlorine at the tap in hospitals housing patients who are at high risk of acquiring nosocomial legionellosis (eg, immunocompromised patients).[385,429,440,447-450] (See Appendix B.) ***CATEGORY II***

iii. *No recommendation* for treatment of water with ozone, ultraviolet light, or heavy-metal ions.[391,460-463,466] ***UNRESOLVED ISSUE***

iv. Clean hot-water storage tanks and waterheaters to remove accumulated scale and sediment.[393] ***CATEGORY IB***

v. Restrict immunocompromised patients from taking showers, and use only sterile water for their oral consumption until *Legionella* spp. become undetectable by culture in the hospital water.[430] ***CATEGORY II***

(b) If cooling towers or evaporative condensers are implicated, decontaminate the cooling-tower system using the protocol outlined in Appendix D.[464] ***CATEGORY IB***

(4) Assess the efficacy of implemented measures in reducing or eliminating *Legionella* spp. by collecting specimens for culture at 2-week intervals for 3 months. ***CATEGORY II***

(a) If *Legionella* spp. are not detected in cultures during 3 months of monitoring, collect cultures monthly for another 3 months. ***CATEGORY II***

(b) If *Legionella* spp. are detected in one or more cultures, reassess the implemented control measures, modify them accordingly, and repeat decontamination procedures. Options for repeat decontamination include the intensive use of the same technique utilized for initial decontamination, or a combination of superheating and hyperchlorination. ***CATEGORY II***

(5) Keep adequate records of all infection control measures, including maintenance procedures, and of environmental test results for cooling towers and potable-water systems. ***CATEGORY II***

PREVENTION AND CONTROL OF NOSOCOMIAL PULMONARY ASPERGILLOSIS

I. Staff Education and Infection Surveillance

A. Staff Education

Educate health-care workers regarding nosocomial pulmonary aspergillosis especially in immunocompromised patients, and about infection control procedures to decrease its occurrence.[659-661] ***CATEGORY IA***

B. Surveillance

1. Maintain a high index of suspicion for the diagnosis of nosocomial pulmonary aspergillosis in high-risk patients, ie, patients with prolonged, severe granulocytopenia (< 1,000 polymorphonuclear cells/mm^3 for 2 weeks or < 100 polymorphonuclear cells/mm^3 for 1 week), most notably bone-marrow transplant recipients.[512,513,709] Consider solid-organ transplant recipients and patients with hematologic malignancies who are receiving chemotherapy also to be at high risk of developing the infection when they are severely granulocytopenic as defined above.[473,485,512,710] ***CATEGORY IB***

2. Maintain surveillance for cases of nosocomial pulmonary aspergillosis by periodically reviewing the hospital's microbiologic, histopathologic, and postmortem data. ***CATEGORY IB***

3. *No recommendation* for performing routine, periodic cultures of the nasopharynx of high-risk patients, or devices, air samples, dust, ventilation ducts, and filters in rooms occupied by high-risk patients.[457,478,487,488,521-523] ***UNRESOLVED ISSUE***

II. Interruption of Transmission of Aspergillus Spp. Spores

A. Planning New Specialized-Care Units for High-Risk Patients

1. When constructing new specialized-care units for high-risk patients, ensure that patient rooms have adequate capacity to minimize fungal spore counts via maintenance of (a) high-efficiency air filtration, (b) directed room airflow, (c) positive air pressure in patient's room in relation to the corridor, (d) properly sealed room, and (e) high rates of room-air changes.[474,529-531,534,538,711,712] ***CATEGORY IB***

a. Air filtration. Install high efficiency particulate air (HEPA) filters that are 99.97% efficient in filtering 0.3μ-sized particles, either centrally or at the point of use, ie, at the room-air intake site.[474,529-531,534,538,711,712] ***CATEGORY IB***

b. Directed room airflow. Place air-intake and exhaust ports such that room air comes in from one side of the room, flows across the patient's bed, and exits on the opposite side of the room.[530,531] ***CATEGORY IB***

c. Well-sealed room. Construct windows, doors, and intake and exhaust ports to achieve complete sealing of the room against air leaks.[530,531] ***CATEGORY IB***

d. Room-air pressure. Ensure that room-air pressure can be maintained continuously above that of corridor, eg, as can be demonstrated by performance of the smoke-tube test, unless there are clinical-care or infection-control contraindications to doing so.[530,531] ***CATEGORY IB***

(1) To maintain positive room-air pressure in relation to the corridor, supply room air at a rate that is 10-20% more than the rate of exhausting air from the room.[530,531] ***CATEGORY IB***

(2) For placement of patients at high risk of aspergillosis who also have an infection (eg, varicella or infectious tuberculosis) requiring negative room-air pressure in relation

to the corridor, provide optimal conditions to prevent the spread of the airborne infection from and acquisition of aspergillosis by the patient, eg, by providing anterooms with an independent exhaust.[530] ***CATEGORY II***

e. Room-air changes. Maintain room-air changes at ≥ 12 per hour.[1,530,536,537] ***CATEGORY II***

2. *No recommendation* for the preferential installation of a particular system, such as one with ultra-high air change rates (100-400 per hour), eg, laminar airflow, over other systems that meet the conditions in II-A-1-a through II-A-1-e above.[474,529-531,534,538,711,712] ***UNRESOLVED ISSUE***

3. Formulate hospital policies to minimize exposures of high-risk patients to potential sources of *Aspergillus* spp., such as hospital construction and renovation, cleaning activities, carpets, food, potted plants, and flower arrangements.[467,487,523,538,713-715] ***CATEGORY IB***

4. *No recommendation* for prophylactic use of copper-8-quinolinolate biocide in fireproofing material.[467,477,531,538] ***UNRESOLVED ISSUE***

B. In Existing Facilities with No Cases of Nosocomial Aspergillosis

1. Place high-risk patients in protected environment that meets the conditions outlined in Section II-A-1-a through II-A-1-e above.[474,487,529,538,711,712,716] ***CATEGORY IB***

2. Routinely inspect air-handling systems in high-risk patient-care areas, maintain adequate air exchanges and pressure differentials, and eliminate air leakages. Coordinate repairs of the system with relocation of high-risk patients to other areas with optimal air-handling capabilities.[467,478,487] ***CATEGORY IB***

3. Minimize the time high-risk patients spend outside their rooms for diagnostic procedures and other activities; and when high-risk patients leave their rooms, require them to wear well-fitting masks capable of filtering *Aspergillus* spp. spores. ***CATEGORY IB***

4. Prevent dust accumulation by daily damp-dusting horizontal surfaces, regularly cleaning ceiling tiles and air-duct grates when the rooms are not occupied by patients, and maintaining adequate seals on windows to prevent room infiltration by outside air, especially in areas occupied by patients at high-risk for developing aspergillosis.[487] ***CATEGORY IB***

5. Systematically review and coordinate infection-control strategies with personnel in charge of hospital engineering, maintenance, central supply and distribution, and catering.[467,523] ***CATEGORY IB***

6. When planning hospital construction and renovation activities, assess whether patients at high-risk for aspergillosis are likely to be exposed to high ambient-air spore counts of *Aspergillus* spp. from construction and renovation sites, and develop a plan to prevent such exposures.[467,523] ***CATEGORY IB***

7. During construction or renovation activities:

(a) Construct barriers between patient-care and construction areas to prevent dust from entering patient-care areas; these barriers, (eg, plastic or drywall) should be impermeable to *Aspergillus* spp.[467,478,522,523] ***CATEGORY IB***

(b) In construction/renovation areas inside the hospital, create and maintain negative pressure relative to that in adjacent patient-care areas if there are no contraindications for such pressure differential, eg, there are patients with infectious tuberculosis in the adjacent patient-care areas.[467,478,522,523,538] ***CATEGORY II***

(c) Direct pedestrian traffic from construction areas away from patient-care areas to limit opening and closing of doors (or other barriers) that may cause dust dispersion, entry of contaminated air, or tracking of dust into patient areas.[467,478,522,523] ***CATEGORY IB***

(d) Clean newly constructed areas before allowing patients to enter the areas.[467,523] ***CATEGORY IB***

8. Eliminate exposures of patients at high-risk for aspergillosis to activities, such as floor or carpet vacuuming, that may cause spores of *Aspergillus* spp. and other fungi to be aerosolized.[467,487,523] ***CATEGORY IB***

9. Eliminate exposures of patients at high-risk for aspergillosis to potential environmental sources of *Aspergillus* spp., such as *Aspergillus*-contaminated food, potted plants, or flower arrangements.[467,487,523,713-715] ***CATEGORY II***

10. Prevent birds from gaining access to hospital air-intake ducts.[524] ***CATEGORY IB***

C. When a Case of Nosocomial Aspergillosis Occurs

1. Begin a prospective search for additional cases in hospitalized patients and an intensified retrospective review of the hospital's microbiologic, histopathologic, and postmortem records. ***CATEGORY IB***

2. If there is no evidence of continuing transmission, continue routine maintenance procedures to prevent nosocomial aspergillosis, as in Section II-B-1 through II-B-10 above. ***CATEGORY IB***

3. If evidence of continuing *Aspergillus* spp. infection exists, conduct an environmental investigation to determine and eliminate the source. If assistance is needed, contact the local or state health department.[474,477,478,522,534,538] ***CATEGORY IB***

a. Collect environmental samples from potential sources of *Aspergillus* spp., especially those sources implicated in the epidemiologic investigation, by using appropriate methods,[474,477,478,522,534,538,717] eg, use of a high-volume air sampler rather than settle plates.[474] ***CATEGORY IB***

b. Perform molecular subtyping of *Aspergillus* spp. obtained from patients and the environment to establish strain identity, depending on test availability.[526,527] ***CATEGORY IB***

c. If air-handling systems supplying high-risk patient-care areas are not optimal, consider temporary deployment of portable HEPA filters until rooms with optimal air-handling systems are available for all patients at high risk of invasive aspergillosis. ***CATEGORY II***

d. If an environmental source is identified, perform corrective measures as needed to eliminate the source from the high-risk patients' environment. ***CATEGORY IB***

e. If an environmental source is not identified, review existing infection-control measures, including engineering aspects, to identify potential areas that can be corrected or improved. ***CATEGORY IB***

III. Modifying Host Risk for Infection

A. Administer cytokines, including granulocyte colony-stimulating factor and granulocyte-macrophage stimulating factor, to increase host resistance to aspergillosis by decreasing the duration and severity of chemotherapy-induced granulocytopenia.[514,515] ***CATEGORY II***

B. *No recommendation* for administration of intranasal amphotericin B or oral antifungal agents (including amphotericin B and triazole compounds) in high-risk patients for prophylaxis against aspergillosis.[516,517,718] ***UNRESOLVED ISSUE***

PREVENTION AND CONTROL OF RESPIRATORY SYNCYTIAL VIRUS INFECTION

I. Staff Education and Infection Surveillance

A. Staff Education

Educate personnel about the epidemiology, modes of transmission and means of preventing spread of respiratory syncytial virus (RSV).[226,659-661] ***CATEGORY IA***

B. Surveillance

1. Establish mechanism(s) by which the appropriate hospital personnel are promptly alerted to any increase in RSV activity in the local community. ***CATEGORY IB***

2. During periods of increased prevalence of RSV in the community (and during December-March), attempt prompt diagnosis of RSV infection by using rapid diagnostic techniques as clinically indicated in pediatric patients, especially infants, and in immunocompromised adults admitted to the hospital with respiratory illness.[593,597] ***CATEGORY IB***

II. Interruption of Transmission of RSV

A. Prevention of Person-to-Person Transmission

1. Primary measures for contact isolation

a. Handwashing

Wash hands after contact with a patient, or after touching respiratory secretions or fomites potentially contaminated with respiratory secretions, whether or not gloves are worn.[218,231,554,584-586,595] ***CATEGORY IA***

b. Gloving

(1) Wear gloves for handling patients or respiratory secretions of patients with proven or suspected RSV infection, or fomites potentially contaminated with patient secretions.[226,554,584,585,591,597] ***CATEGORY IA***

(2) Change gloves between patients, or after handling respiratory secretions or fomites contaminated with secretions from one patient before contact with another patient.[226,228] Wash hands after removing gloves. (See II-A-1-a, above.) ***CATEGORY IA***

c. Gowning

Wear a gown when soiling with respiratory secretions from a patient is anticipated, eg, when handling infants with RSV infection or other viral respiratory illness, and change the gown after such contact and before caring for another patient.[226,590,592,597] ***CATEGORY IB***

d. Staffing

Restrict health-care workers in the acute stages of an upper respiratory illness (ie, those who are sneezing and/or coughing) from taking care of infants and other patients at high risk for complications from RSV infection (eg, children with severe underlying cardio-pulmonary conditions, children receiving chemotherapy for malignancy, premature infants, and patients who are otherwise immunocompromised).[595,597] ***CATEGORY IB***

e. Limiting visitors

Do not allow persons with symptoms of respiratory infection to visit pediatric, immunosuppressed, and cardiac patients.[591] ***CATEGORY II***

2. Control of RSV Outbreaks

a. Use of private room, cohorting, and patient-screening

To control ongoing RSV transmission in the hospital, admit young children with symptoms of viral respiratory illness to single rooms when possible, OR perform RSV-screening diagnostic tests on young children upon admission and cohort them according to their RSV-infection status.[591,593,595,597] ***CATEGORY II***

b. Personnel cohorting

During an outbreak of nosocomial RSV, cohort personnel as much as practical, ie, restrict personnel who give care to infected patients from giving care to uninfected patients, and vice-versa.[591,595,597] ***CATEGORY II***

c. Postponing patient admission

During outbreaks of nosocomial RSV, postpone elective admission of uninfected patients at high risk of complications from RSV infection. ***CATEGORY II***

d. Wearing eye-nose goggles

No recommendation for wearing eye-nose goggles for close contact with an RSV-infected patient.[594,598] ***UNRESOLVED ISSUE***

PREVENTION AND CONTROL OF INFLUENZA

I. Staff Education and Infection Surveillance

A. Staff Education

Educate personnel about the epidemiology, modes of transmission, and means of preventing the spread of influenza.[659-661,719,720] ***CATEGORY IA***

B. Surveillance

1. Establish mechanism(s) by which the appropriate hospital personnel are promptly alerted of any increase in influenza activity in the local community. ***CATEGORY IB***

2. Arrange for laboratory tests to be available to clinicians, for use when clinically indicated, to promptly confirm the diagnosis of influenza and other acute viral respiratory illnesses, especially during November- April.[620-625] ***CATEGORY IB***

II. Modifying Host Risk to Infection

A. Vaccination

1. Patients

Offer vaccine to outpatients and inpatients at high risk of complications from influenza, beginning in September and continuing until influenza activity has begun to decline.[628,631,648,721-723] Patients at high risk of complications from influenza include those ≥ 65 years of age; in long-term-care units; with chronic disorders of the pulmonary or cardiovascular systems, diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression; and children 6 months-18 years of age who are receiving long-term aspirin therapy.[628] In addition, consider patients with musculo-skeletal disorders that impede adequate respiration to be at risk of complications from influenza. ***CATEGORY IA***

2. Personnel

Vaccinate health-care workers before the influenza season each year, preferably between mid-October and mid-November. Until influenza activity declines, continue to make vaccine available to newly hired personnel and to those who initially refuse vaccination. If vaccine supply is limited, give highest priority to staff caring for patients at greatest risk of severe complications from influenza infection, as listed in Section II-A-1 above.[628] ***CATEGORY IB***

B. Use of Antiviral Agents (See Section IV below, Control of Influenza Outbreaks)

III. Interruption of (Person-to-Person) Transmission

A. Keep a patient for whom influenza is suspected or diagnosed in a private room, or in a room with other patients with proven influenza, unless there are medical contraindications to doing so. ***CATEGORY IB***

B. As much as feasible, maintain negative air pressure in rooms of patients for whom influenza is suspected or diagnosed, or place together persons with influenza-like illness in a hospital area with an independent air-supply and exhaust system.[614,615,617,724] ***CATEGORY II***

C. Institute masking of individuals (except

those immune to the infecting strain) who enter the room of a patient with influenza.[614,615,724] ***CATEGORY IB***

D. As much as possible during periods of influenza activity in the community, have the hospital's employee health service evaluate patient-care staff who have symptoms of febrile upper respiratory tract infection suggestive of influenza for possible removal from duties that involve direct patient contact. Use more stringent guidelines for staff working in certain patient-care areas, eg, ICUs, nurseries, and units with severely immunosuppressed patients.[649,725] ***CATEGORY II***

E. When community and/or nosocomial outbreaks occur, especially if they are characterized by high attack rates and severe illness:

1. Restrict hospital visitors who have a febrile respiratory illness. ***CATEGORY IB***

2. Curtail or eliminate elective medical and surgical admissions as necessary. ***CATEGORY IB***

3. Restrict cardiovascular and pulmonary surgery to only emergency cases. ***CATEGORY IB***

IV. Control of Influenza Outbreaks

A. Determining the Outbreak Strain

Early in the outbreak, obtain nasopharyngeal-swab or nasal-wash specimens from patients with recent-onset symptoms suggestive of influenza for influenza virus culture or antigen detection. ***CATEGORY IB***

B. Vaccination of Patients and Personnel

Administer current influenza vaccine to unvaccinated patients and staff, especially if the outbreak occurs early in the influenza season.[610,628] ***CATEGORY IB***

C. Amantadine or Rimantadine Administration

1. When a nosocomial outbreak of influenza A is suspected or recognized:

a. Administer amantadine or rimantadine for prophylaxis to all uninfected patients in the involved unit for whom it is not contraindicated. Do not delay administration of amantadine or rimantadine unless the results of diagnostic tests to identify the infecting strain(s) can be obtained within 12 to 24 hours after specimen collection.[634,642] ***CATEGORY IB***

b. Administer amantadine or rimantadine for prophylaxis to unvaccinated staff members for whom it is not medically contraindicated, and who are in the involved unit or taking care of high-risk patients.[642] ***CATEGORY II***

2. Discontinue amantadine or rimantadine if laboratory tests confirm or strongly suggest that influenza type A is not the cause of the outbreak.[632] ***CATEGORY IA***

3. If the cause of the outbreak is confirmed or believed to be influenza type A AND vaccine has been administered only recently to susceptible patients and personnel, continue amantadine or rimantadine prophylaxis until 2 weeks after the vaccination.[726] ***CATEGORY IB***

4. To the extent possible, do not allow contact between those at high risk of complications from influenza and patients or staff who are taking amantadine or rimantadine for treatment of acute respiratory illness; prevent contact during and for two days after the latter discontinue treatment.[633,643-647] ***CATEGORY IB***

D. Interruption of (Person-to-Person) Transmission of Microorganisms (See Section III, A-E above.)

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APPENDIX A

EXAMPLES OF SEMICRITICAL ITEMS* USED ON THE RESPIRATORY TRACT

Anesthesia device or equipment including:
- face mask or tracheal tube
- inspiratory and expiratory tubing
- Y-piece
- reservoir bag
- humidifier

Breathing circuits of mechanical ventilators
Bronchoscopes and their accessories, except for biopsy forceps and specimen brush, which are considered critical items and are sterilized before reuse.
Endotracheal and endobronchial tubes
Laryngoscope blades
Mouthpieces and tubings of pulmonary function testing equipment
Nebulizers and their reservoirs
Oral and nasal airways
Probes of CO_2 analyzers, air-pressure monitors
Resuscitation bags
Stylets
Suction catheters
Temperature sensors

*Items that directly or indirectly contact mucous membranes of the respiratory tract. They are sterilized or subjected to high-level disinfection before reuse.

APPENDIX B

MAINTENANCE PROCEDURES TO DECREASE SURVIVAL AND MULTIPLICATION OF *LEGIONELLA* SPP. IN POTABLE-WATER DISTRIBUTION SYSTEMS

1. Providing Water at ≥ 50°C at All Points in the Heated Water System, Including the Taps

This requires that water in calorifiers (water heaters) be maintained at ≥ 60°C. In the United Kingdom, where maintenance of tap-water temperatures at ≥ 50°C in hospitals has been mandated, installation of blending or mixing valves at or near taps to reduce the water temperature to ≤ 43°C has been recommended in certain settings to reduce the risk of scald injury to patients, visitors, and health-care workers.[447] However, *Legionella* spp. can multiply even in short segments of pipe containing water at this temperature. Increasing the flow rate from the hot-water-circulation system may help lessen the likelihood of water stagnation and cooling.[450,727] Insulation of plumbing to ensure delivery of cold (< 20°C) water to water heaters (and to cold-water outlets) may diminish the opportunity for bacterial multiplication.[392] "Dead legs" or capped spurs within the plumbing system provide areas of stagnation and cooling to < 50°C regardless of the circulating-water temperature; these segments may

need to be removed to prevent colonization.[728] Rubber fittings within plumbing systems have been associated with persistent colonization, and replacement of these fittings may be required for *Legionella* spp. eradication.[729]

II. Continuous Chlorination To Maintain Concentrations of Free Residual Chlorine at 1-2 mg/L at the Tap

This requires the placement of flow-adjusted, continuous injectors of chlorine throughout the water distribution system. Adverse effects of continuous chlorination include accelerated corrosion of plumbing resulting in system leaks and production of potentially carcinogenic trihalomethanes. However, when levels of free residual chlorine are below 3 mg/L, trihalomethane levels are kept below the maximum "safety level" recommended by the Environmental Protection Agency.[448,730,731]

APPENDIX C

CULTURING ENVIRONMENTAL SPECIMENS FOR *LEGIONELLA* SPP.

I. Recommended Procedure for Collecting and Culturing Environmental Specimens for Legionella Spp.[732]

A. Collect water (if possible, one-liter samples) in sterile, screw-top bottles, preferably containing sodium thiosulfate at a concentration of 0.5 cc of 0.1N solution of sample water. (Sodium thiosulfate inactivates any residual halogen biocide).

B. Collect culture-swabs of the internal surfaces of faucets, aerators, and showerheads; in a sterile, screw-top container, such as a 50-cc plastic centrifuge tube, submerge each swab in 5-10 cc of sample water taken from the same device from which the sample was obtained.

C. As soon as possible after collection, water samples and swabs should be transported to and processed in a laboratory proficient at culturing water specimens for *Legionella* spp. Samples may be transported at room temperature but must be protected from temperature extremes.

D. Test samples for the presence of *Legionella* spp. by using semi-selective culture media. Use standard laboratory procedures. (Detection of *Legionella* spp. antigen by the direct fluorescent antibody technique is not suitable for environmental samples.[733-735] In addition, the use of polymerase chain reaction (PCR) for identification of *Legionella* spp. is not recommended until more data on the sensitivity and specificity of this procedure are available.[736]

II. Possible Samples and Sampling Sites for Legionella Spp. in the Hospital[737]

Water Samples

- Potable Water System
  - Incoming water main
  - Water softener
  - Holding tanks/cisterns
  - Water heater tanks (inflow and outflow sites)
  - Potable water outlets (faucets or taps, showers) especially outlets located in or near case-patients' rooms
- Cooling Tower/Evaporative Condenser
  - Make-up water (water added to system to replace water lost by evaporation, drift, and leakage
  - Basin (area under tower for collection of cooled water)
  - Sump (section of basin from which cooled water returns to heat source)
  - Heat source (eg, chillers)
- Other Sources
- Humidifiers (Nebulizers)
  - Bubblers for oxygen
  - Water used for respiratory therapy equipment
  - Decorative fountains
  - Irrigation equipment
  - Fire sprinkler system (if recently used)
  - Whirlpools/spas

Swabs

- Potable Water System
  - Faucets (proximal to aerators)
  - Faucet aerators
  - Shower heads
- Cooling Towers
  - Internal components (eg, splash bars and other fill surfaces)
  - Areas with visible biofilm accumulation

APPENDIX D

PROCEDURE FOR CLEANING COOLING TOWERS AND RELATED EQUIPMENT

(Adapted from the Emergency Protocol in Control of *Legionella* spp. in Cooling Towers: Summary Guidelines.[464])

I. Preparatory to Chemical Disinfection and Mechanical Cleaning

A. Provide protective equipment to workers who would perform the disinfection, to prevent their exposure to (a) chemicals used for disinfection and (b) aerosolized water containing *Legionella* spp. Protective equipment may include full-length protective clothing, boots, gloves, goggles, and a full- or half-face mask that combines high efficiency particulate air filter and chemical cartridges to protect against airborne chlorine levels of up to 10 mg/L.

B. Shut off cooling-tower.

1. If possible, shut off heat source.

2. Shut off fans, if present, on the cooling tower/evaporative condenser (CT/EC).

3. Shut off the system blowdown (purge) valve. Shut off automated blowdown controller, if present, and set system controller to manual.

4. Keep make-up water valves open.

5. Close building air-intake vents within at least 30 meters of the CT/EC until after the cleaning procedure is complete.

6. Continue operating pumps for water circulation through the CT/EC.

II. Chemical Disinfection

A. Add fast-release, chlorine-containing disinfectant in pellet, granular, or liquid form, and follow safety instructions on the product label. Examples of disinfectants include sodium hypochlorite (NaOCl) or calcium hypochlorite $Ca[OCl]_2$ calculated to achieve initial free residual chlorine (FRC) of 50 mg/L, ie, 3.0 lbs (1.4 kg) industrial grade NaOCl (12-15% available Cl) per 1,000 gallons of CT/EC water; 10.5 lbs (4.8 kg) domestic grade NaOCl (3-5% available Cl) per 1,000 gallons of CT/EC water; or 0.6 lb (0.3 kg) $Ca(OCl)_2$ per 1,000 gallons of CT/EC water. If significant biodeposits are present, additional chlorine may be required. If the volume of water in CT/EC is not known, it can be estimated (in gallons) by multiplying the recirculation rate in gallons/minute by 10, or the refrigeration capacity in tons by 30. Other appropriate compounds may be suggested by a water-treatment specialist.

B. Record the type and quality of all chemicals used for disinfection, exact time the chemicals are added to the system, and time and results of measurements of FRC and pH.

C. Add dispersant simultaneously with or within 15 minutes of adding disinfectant. The dispersant is best added by first dissolving it in water and adding the solution to a turbulent zone in the water system. Examples of low or non-foaming, silicate-based dispersants are: automatic-dishwasher compounds, such as Cascade* or Calgonite* or an equivalent product. Dispersants are added at 10-25 lbs. (4.5-11.25 kg) per 1,000 gallons of CT/EC water.

D. After adding disinfectant and dispersant, continue circulating the water through the system. Monitor FRC by using an FRC-measuring device, such as a swimming pool test kit, and measure the pH with a pH meter every 15 minutes for 2 hours.

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*The use of product names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Add chlorine as needed to maintain FRC at ≥ 10 mg/L. Since the biocidal effect of chlorine is reduced at higher pH, adjust pH to 7.5-8.0. The pH may be lowered by using any acid (eg, muriatic acid or sulfuric acid used for maintenance of swimming pools) that is compatible with the treatment chemicals.

E. Two hours after adding disinfectant and dispersant or after FRC level is stable at ≥ 10 mg/L, monitor at 2-hour intervals and maintain FRC at ≥ 10 mg/L for 24 hours.

F. After FRC level has been maintained at ≥ 10 mg/L for 24 hours, drain the system. CT/EC water may be safely drained to the sanitary sewer. Municipal water and sewerage authorities should be contacted regarding local regulations. If a sanitary sewer is not available, consult local or state authorities (eg, Department of Natural Resources) regarding disposal of water. If necessary, the drain-off may be dechlorinated by dissipation or by chemical neutralization with sodium bisulfite.

G. Refill system with water and repeat procedure outlined in steps 2-6 in I-B above.

III. Mechanical Cleaning

A. After water from the second chemical disinfection has been drained, shut down the CT/EC.

B. Inspect all water contact areas for sediment, sludge, and scale. Using brushes and/or a low-pressure water hose, thoroughly clean all CT/EC water contact areas including basin, sump, fill, spray nozzles, and fittings. Replace components as needed.

C. If possible, clean CT/EC water contact areas within the chillers.

IV. After Mechanical Cleaning

A. Fill the system with water, and add chlorine to achieve FRC level of 10 mg/L.

B. Circulate the water for one hour, then open blowdown valve and flush the entire system until the water is free of turbidity.

C. Drain the system.

D. Open any air intake vents that were closed prior to cleaning.

E. Fill the system with water. CT/EC may be put back into service using an effective water-treatment program.

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A comparison of the imposed work of breathing with endotracheal and tracheostomy tubes in a lung model [Davis et al] **39(6):611** *research article*

Nosocomial cutaneous mucormycosis at the site of endotracheal tube taping [Amundson et al] **39(9):917** *letter*

Tubes, Tracheostomy: ***Also see*** **Airway Care & Management**

A comparison of the imposed work of breathing with endotracheal and tracheostomy tubes in a lung model [Davis et al] **39(6):611** *research article*

Upper-Airway Disorders

Delivery of aerosols to the upper airway **39(8):803** *Clinical Practice Guideline*

Ventilator Circuits: ***Also see*** **Equipment & Supplies**

Guideline for prevention of nosocomial pneumonia [CDC] **39(12):1191** *guideline*

Guideline for prevention of nosocomial pneumonia and ventilator circuits: time for a change? [Hess] **39(12):1149** *editorial*

Managing the patient-ventilator system: system checks and circuit changes [Campbell] **39(3):227** *symposium paper*

Ventilator circuit changes **39(8):797** *Clinical Practice Guideline*

Vocal Cord Dysfunction

Idiopathic vocal cord paralysis in a newborn infant: a case report [Douglas & Polamreddy] **39(6):630** *case report*

Weaning

Indications and criteria for decannulation and transition from invasive to noninvasive long-term ventilatory support [Bach & Saporito] **39(5):515** *conference proceedings*

Negative pressure ventilation for facilitation of weaning from mechanical ventilation—back to the future? [Hill] **39(1):19** *editorial*

Routine measurement of work of breathing: is it necessary? [Kacmarek & Hess] **39(9):881** *editorial*

Transition from the intensive care unit to home: patient selection and discharge planning [Gilmartin] **39(5):456** *conference proceedings*

Use of extrathoracic negative pressure ventilation in weaning COPD and kyphoscoliotic patients from mechanical ventilation [Del Bufalo et al] **39(1):21** *research article*

Work of breathing: how to define and when to measure? [Adams] **39(9):883** *editorial*

Work of Breathing

A comparison of CPAP performance characteristics of the Puritan-Bennett 7200a and a prototype continuous pressure-regulating ventilator [Tobia & Fischer] **39(3):195** *research article*

A comparison of the imposed work of breathing with endotracheal and tracheostomy tubes in a lung model [Davis et al] **39(6):611** *research article*

Decreasing the work of breathing: how much of a change is important? [Branson] **39(3):187** *editorial*

Flow-triggering does not decrease the work of breathing and pressure-time product in COPD patients [Jager et al] **39(9):892** *research article*

A new respiratory monitor that enables accurate measurement of work of breathing: a validation study [Blanch & Banner] **39(9):897** *research article*

Routine measurement of work of breathing: is it necessary? [Kacmarek & Hess] **39(9):881** *editorial*

Work of breathing: how to define and when to measure? [Adams] **39(9):883** *editorial*

Books, Films, Tapes, & Software

Listing and Reviews of Books and Other Media
Note to publishers: Send review copies of books, films, tapes, and software to RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Therapeutics in Respiratory Disease, by Peter J Barnes MA DM DSc, Kian Fan Chung MD, Timothy W Evans MD PhD, and Stephen G Spiro MD, with a contribution by Robert F Miller MB BS. Hardcover, 174 pages with index, 30 illustrations. London: Churchill Livingstone, 1994. $59.95.

Therapeutics in Respiratory Disease is an interesting and informative text by Dr Peter Barnes and colleagues, which, in the words of the authors, "describes the drug treatments currently available for the management of lung diseases, and also gives some consideration to new treatments under development." The rationale for such a text is well founded. New drugs have been introduced to treat lung diseases, uses of old drugs have changed, and understanding of the disease processes themselves is increasing, which ultimately affects the treatment. The authors cite asthma as an example—where an appreciation of the inflammatory nature of the disease has led to the use of inhaled corticosteroids as first-line therapy. The text is not a book about pulmonary diseases or pharmacology alone but rather a melding of the two topics into a presentation on the use of various drugs and drug groups in the treatment of lung diseases. In this respect, the book complements and advances those two topics—presented separately in many curricula—as a single integrated subject.

The authors offer the hope that the text will be useful for respiratory physicians (a specialty beyond the introductory medical level), clinical pharmacologists, and researchers involved in lung diseases. To that list should be added respiratory care practitioners. Although the book is advanced for respiratory therapy students, an effort to comprehend the material would be rewarded with a better, more integrated understanding of drug therapy and lung diseases. In particular, the authors concisely discuss drug therapy of lung diseases other than chronic obstructive pulmonary disease (COPD) and tuberculosis (eg, pulmonary vascular disease and lung cancer). The book would be a valuable reference for educators and serious practitioners who wish to advance their knowledge. Because the text combines the two subjects of pulmonary disease and pharmacology into an application of drug therapy in managing lung disease, some background knowledge of these two subjects is helpful. From a practical point of view, it may be difficult to use the text in the curriculum of a respiratory care program in which topics typically are introduced in a compartmentalized fashion.

When the American reader considers this book, it is important to note that all of the authors are practicing in the United Kingdom (U.K.), and are presenting respiratory medicine outside of the United States. This affects drug names as well as spelling of medical terms. For example, instead of the more familiar names of epinephrine, isoproterenol, and albuterol, one reads adrenaline, isoprenaline, and salbutamol. However, this can broaden the horizon of the American reader, a beneficial side effect. For the reader unfamiliar with British spellings, be prepared to see 'nebulised' instead of 'nebulized,' 'oedema' for 'edema,' and 'hypoxaemia' rather than 'hypoxemia.' Drugs are also mentioned that are not currently available in the United States, including the long-acting beta-$_2$ agonist formoterol, some of the inhaled corticosteroids such as betamethasone maleate and fluticasone propionate, as well as antituberculosis drugs, thiacetazone and prothionamide. Differences are also found in terminology used for oxygen delivery equipment. In Chapter 3, "Respiratory Failure," the terms "fixed performance devices" and "variable performance devices" are used to denote the American categories of high-flow and low-flow oxygen delivery devices, respectively. An example of a fixed performance device is given by the venturi mask, and the variable performance device with the nasal cannula and the simple oxygen mask. The examples and description of performance should allow the American practitioner to quickly translate the difference in terminology without undue confusion.

Although the book is written by more than one author, it avoids problems that often occur with multiple writers. This is facilitated by the fact that all of the authors work at the same hospital in London (Royal Brompton National Heart and Lung Hospital). Specifically, the authors use a consistent organizational style, with a chapter contents outline at the beginning of every chapter, and figures, tables, and boxes prepared with a uniform appearance. This contributes greatly to a clean, clear format and maintains the clarity of organization needed with contributions from multiple authors. The book consists of 9 chapters, with the first chapter providing an eclectic but highly informative overview of pharmacologic principles and concepts, with examples and application to drugs used in the treatment of lung disease. In particular, the in-depth presentation of drug-receptor interactions (pharmacodynamics) is well done and extremely useful for respiratory care. Subsequent chapters are each devoted to a disease state. Chapter 2 deals with obstructive airway diseases (asthma, chronic obstructive pulmonary disease); Chapters 3 through 10 discuss respiratory failure, respiratory infections, infections in AIDS, tuberculosis, lung cancer, pulmonary vascular disease, cough and breathlessness, and drug-induced pulmonary disease, respectively. In particular, illustrations are well done and of uniform style, and they complement the textual presentation.

The term therapeutics, in the title of the book, is actually broadened to include modes of support as well as drugs. In Chapter 3, it is interesting to see oxygen recognized as a drug and modes of delivery reviewed. Oxygen therapy is in fact a broader topic than drug therapy because medical gas therapy not only includes the agent itself but the mode of delivery, which can be an additional form of therapeutic support. For example, continuous positive airway pressure (CPAP) is presented in the discussion of oxygen therapy. This form of support adds pressure to the oxygen, and one could argue that this is a mode of support and not just a form of drug therapy. Similarly, in Chapter 8, "Pulmonary Vascular Disease," the authors discuss modes of ventilatory support such as pressure-control inverse-ratio ventilation, volume-controlled inverse-ratio ventilation, and extracorporeal gas exchange for treating adult respiratory distress syndrome (ARDS), in addition to pharmacologic inter-

vention. Nonetheless, the primary emphasis throughout the text is on drug therapies of lung diseases, fulfilling the stated goal of the authors in the Preface.

The accuracy and quality of the book appear to be superior. However, some deficiencies were noted. In Chapter 2, "Obstructive Airway Disease," the term 'chronic obstructive airways disease,' or COAD, is used; whereas Chapter 3, "Respiratory Failure," introduces 'chronic obstructive pulmonary disease,' or COPD. In Chapter 2, COAD is actually identified as emphysema and specifically does not include chronic bronchitis. The relation or difference between COPD and COAD is not made clear by the authors. This may be a weakness of multiple authorship that was not totally avoided. Other deficiencies may reflect the lack of an identifiable respiratory care profession with specialized education in the U.K. An example is seen in a diagram for continuous positive airway pressure, or CPAP, in Chapter 3 (Figure 3.2). A flowmeter is used with a "flow generator," which humidifies the gas and entrains additional gas, to provide a total flow of 70-80 L/min. Unless some other type of flow generator is intended but not identified, this is not correct. Air entrainment does not occur in a pressurized system, as every therapist well knows. Similarly, two pressure graphs in a figure in Chapter 8 (Figure 8.2) are identified as "inverse ratio ventilation and airway pressure-release ventilation." Neither pressure curve describes APRV but rather two variably increasing inspiratory pressure levels with an inspiratory hold, giving greater inspiratory than expiratory times. Other errors are almost certainly typographical: Arterial oxygen tension is noted as P_{aCO_2}, both in the text of Chapter 3 and in a table (Box 3.1).

Finally, some statements appear overly authoritative and, given the ever-changing environment of medical science, verge on the dogmatic. For example in Chapter 2, on Page 14, the statement is made "Chronic bronchitis implies mucus hypersecretion and is not associated with airflow obstruction."

These last comments do not imply that the book is of inferior quality or not of value. I would recommend the text for all respiratory care practitioners, to broaden our knowledge of drug therapy for lung diseases, especially those other than asthma and COPD. Respiratory care students could well be introduced to this text before completing formal coursework, although cost and curricular time are undeniable constraints. The text would be very useful for graduate study at a master's degree level.

Joseph L Rau Jr PhD RRT
Professor and Chair
Cardiopulmonary Care Sciences
Georgia State University
Atlanta, Georgia

Pharmacology and Therapeutics in Respiratory Care, by Theodore J Witek Jr DrPH and E Neil Schachter MD. Hardcover 465 pages, illustrated Philadelphia: WB Saunders Co, 1994. $39.95.

This is a collaborative work involving 19 consulting editors, among them Dr Irwin Ziment, who wrote the first comprehensive text on respiratory pharmacology (published in 1978), and who has supplied a foreword to this book. As he states, this text is now the most authoritative compendium of its type, an assertion with which I would fully agree. The contents are divided into three parts, the first on basic pharmacology and therapeutics, the second on the classes of respiratory drugs, and the third on clinical applications and applied research.

Part I begins with the basic definitions of pharmacokinetics, pharmacodynamics, and pharmacotherapy. The ensuing chapters are specialized, dealing with aerosol delivery, bronchial physiology, mucokinetics, and airway immunology. Part II comprises about half the volume, describing in detail the properties and uses of adrenergic agents, antimuscarinic drugs, methylxanthines, corticosteroids, mucolytics, antitussives, antihistamines, and antimicrobial agents employed in respiratory medicine. At the close of the section a chapter on new, emerging, and experimental therapies is provided. Part III contains three chapters on rather diverse subjects. The first (Chapter 14) considers the main pathophysiologic changes encountered in bronchopulmonary disease and the clinical tests employed to evaluate responses to pharmacotherapy. The second (Chapter 15) discusses airway challenge tests. The third chapter of Part III and last chapter of the book, "Critical Care Pharmacology" (Chapter 16), is a 20-page review of cardiocirculatory failure and a summary of the cardiovascular drugs used in life-threatening conditions. In such a brief discussion, there can be no more than limited reference to the pharmacodynamics, toxicities, and contraindications of drugs affecting the heart and circulation. An adequate bibliography is provided, however.

A few useful appendices are included that relate to prescription writing and dose calculation. These may be of especial benefit to the respiratory care practitioner. Of particular note is the accuracy of the structural formulas of the drugs; the only error noted is the spelling of *bipyridines* (Page 434).

The text is quite readable, and is liberally supplemented with tables and charts defining therapeutic regimens. The work is too large and detailed to be practicable for pharmacology courses in respiratory care programs. However, instructors in such courses will be completely informed through careful study of each chapter. As a reference source for physicians, nurses, and therapists involved in respiratory and critical care, the book is unsurpassed.

Hugh S Mathewson MD
Professor Emeritus of Anesthesiology
Professor of Respiratory Care Education
University of Kansas Medical Center
Kansas City, Kansas

AARC's 1995 Professor's Rounds in Respiratory Care

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Part I • The New JCAHO Hospital Standards: Their Effect on Respiratory Care

March 28, 12:30 p.m. to 2 p.m. Eastern Time—Nancy Telford, RRT with Moderator Sam P. Giordano, MBA, RRT

The new *1995 Accreditation Manual for Hospitals* is now organized around important functions that impact patient outcomes. With this redesign, the standards previously contained in the Respiratory Care Services Chapter are integrated into the functional chapters. Through this overview, viewers will learn about standards related to competence programs, responsibilities of department leaders and medical directors, and expectations on performance improvement. This presentation will also review the interactive survey process and the role of department staff.

Part II • Prevention and Management of Ventilator-Induced Lung Injury

April 25, 12:30 p.m. to 2 p.m. Eastern Time—David J. Pierson, MD with Moderator Richard D. Branson, RRT

There is increasing evidence that the way we manage mechanical ventilation affects the incidence and severity of parenchymal lung injury as well as traditional forms of barotrauma such as pneumothorax and bronchopleural fistula. This presentation will review the data from both animal experiments and clinical experience, and will describe our current concepts of the pathophysiology of ventilator-induced lung injury. It will also cover practical matters such as how to identify patients at increased risk of barotrauma, measures to decrease the likelihood of this complication, and the approach to management of bronchopleural fistula in the ventilated patient.

Part III • The Multidisciplinary Team Approach and Respiratory Care

June 20, 12:30 p.m. to 2 p.m. Eastern Time— Kevin L. Shrake, MA, RRT, CHE with Sam P. Giordano, MBA, RRT

This program will focus on what respiratory care practitioners must do to demonstrate value and create opportunity in the changing environment of health care. Strategies will be outlined on how to develop a professional skills inventory that enhances value and solidifies job security. Restructuring concepts will be presented that focus on developing the multiskilled practitioner capable of functioning on a variety of teams throughout the continuum of health care. Advice will also be provided for managers who want to position themselves as a member of a new breed of "clinical executives" who will guide the future of integrated health care delivery systems in the United States.

Part IV • Emergency Respiratory Care: The Respiratory Care Practitioner's Role

July 19, 12:30 p.m. to 2 p.m. Eastern Time—Charles G. Durbin, Jr., MD, FCCM with Richard D. Branson, RRT

As caregiver roles continue to blur, many new tasks will fall to the most prepared individual in the emergency care setting, regardless of profession. Emergency defibrillation, establishment of intravenous access, and IV and endotracheal drug administration are several areas in which RCPs can become competent. This session will review some of the new approaches to emergency care, "tricks of the trade" in airway maintenance, and changes in the ACLS philosophy and treatment protocols. Methods to increase RCP participation in the hospital emergency response team and the obstacles that they must overcome will be presented.

Part V • Noninvasive Mechanical Ventilation: Its Role in Acute and Chronic Ventilatory Failure

August 2, 12:30 p.m. to 2: p.m. Eastern Time—Nicholas S. Hill, MD with Richard D. Branson, RRT

Although techniques of noninvasive mechanical ventilation (assisting alveolar ventilation without an artificial endotracheal airway) have been with us for decades, recent developments have greatly increased their applicability. This presentation will briefly review the history of noninvasive ventilation, describe modalities of noninvasive ventilation currently available, and discuss the advantages and disadvantages of the various types. Results of studies on acute and chronic respiratory failure will be reviewed and acceptable indications for use of noninvasive ventilation will be described. Considerations for selecting appropriate patients and techniques of initiation and monitoring of noninvasive ventilation will also be discussed.

Part VI • Organizing a Respiratory Care Department without Walls

September 19, 12:30 p.m. to 2 p.m. Eastern Time—John R. Walton, MBA, MHA, RRT, CHE with Sam P. Giordano, MBA, RRT

With hospitals reengineering in advance of federal health reform, the successful respiratory care service must be poised to follow the flow of the patient from the acute hospital through alternate sites. Providing respiratory care in skilled nursing facilities, ambulatory clinics, and the home will require a new breed of respiratory care practitioner willing and able to advance beyond the acute care hospital walls. This "Professor's Rounds" will discuss how to establish respiratory services in the post-acute setting using examples of a successful respiratory care service established in a subacute, skilled nursing facility.

Part VII • Shortening Length of Stay on Ventilators and in Hospitals

November 14, 12:30 p.m. to 2 p.m. Eastern Time—Neil R. MacIntyre, MD with Richard D. Branson, RRT

This program will focus on the reasons patients remain ventilator dependent and the disease specific factors of ventilatory muscle overload, neurological dysfunction, and gas exchange difficulties as well as a discussion of maximizing therapy for the underlying cardiorespiratory disease as a component in shortening the patient's length of stay. The program will also discuss ventilation management issues and complications such as pneumothorax, imposed work from ventilator settings and equipment, aspiration pneumonia, nutrition, and fluid balance that can all contribute to unnecessary duration of mechanical ventilatory support.

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Much of the support you give to the AARC goes toward advancement of the profession. For instance, did you know that through the efforts of the AARC:

Over two-thirds of the states now require that respiratory care practitioners become legally credentialed by the state. These laws, which protect patients and practitioners alike, were passed because of hard work by the AARC and its members.

We assisted the federal government in gathering information on the costs of hospital versus home respiratory care. Our involvement in projects like this strengthens our image in Washington as patient advocates.

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The foremost science journal in the respiratory care profession, publishing original research, case reports, book critiques, letters, and monthly features on chest radiographs, pulmonary function tests, and blood gas analysis.

AARC Times Magazine

The premier news and feature magazine of the profession with management tips, educational articles, human interest features, how-to articles, and reports on current government trends.

AARC Report

A monthly newsletter with fast-breaking news about the Association and other professional activities.

Government Representation

A full-time director of government affairs works for you in Washington, DC, and helps the Association leaders plan strategies for introducing legislation and influencing regulatory activities on reimbursement issues, research projects, consumer protection, smoking laws and more.

State Government Affairs

The AARC's director of state government affairs works with the AARC's affiliates to bring licensure on-line in all 50 states and to help strengthen current acts. The AARC supports its chartered affiliates financially in these endeavors through grant and loan programs. In addition, emphasis is placed on assisting with other issues on the state level. These include health reform bills, laboratory issues, long-term care, and Medicaid concerns.

Continuing Education

The continuing Respiratory Care Education (CRCE) system approves and accredits educational programs and provides you with a transcript of all your continuing education activities to use as proof of attendance at educational meetings.

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Individual Independent Study Packages are self- study modules on 30 different clinical topics. Topics on clinical practice, as well as a series on smoking cessation, are featured.

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No-cost and low-cost insurance programs are part of AARC membership. You receive $10,000 of accidental death and dismemberment insurance free, and you receive discounts on professional liability insurance.

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Joining the AARC gives you access to your state society for respiratory care. In this way you get to know other professionals in your area.

Promotional Support

Promotional items for distribution at health fairs are made available at discounted prices.

Respiratory Care Week

Each year, the Association sponsors a national recognition week for its practitioners. During this week, hospitals recognize the work of respiratory care practitioners throughout the year, and, in addition, many RC departments sponsor special activities for the public to help raise the profile of the profession.

Specialty Sections

For a nominal fee, you may join a specialty section of the AARC. You can choose sections on management, education, adult acute respiratory care, cardiopulmonary science, perinatal-pediatrics, continuing care/ rehabilitation, transport, or home care.

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Discounts are extended to members wishing to order ECRI's publication, Technology for Respiratory Therapy. AARC members pay $45 for an annual subscription, one-half off the usual subscription price.

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AARC meetings bring you up-to-date on the state-of-the-art in respiratory care. AARC members receive a discount to all of these meetings sponsored by the AARC — including the Annual Convention.

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The AARC prepares and publishes reports on a variety of research activities.

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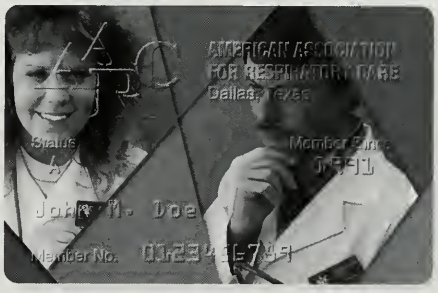

Standards

The AARC, as a standard-setting organization, makes available copies of the position statements and standards it writes.

Clinical Practice Guidelines

Recognizing that our health care system will require even more accountability and validity in the future, the AARC has embarked on a multi-year project to write clinical practice guidelines for all respiratory care modalities.

Product Discounts

The AARC regularly reviews products available for the respiratory care professional and negotiates discounted rates for the member.

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Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

The American Respiratory Care Foundation Announces Literary Awards for 1994

Dr Allen DeVilbiss Award

Best paper published from November 1993 through October 1994 that addresses new technology or a new application of current technology in respiratory care ($2,000 cash plus travel expenses to the AARC Annual Meeting to receive the award)

A New Respiratory Monitor That Enables Accurate Measurement of Work of Breathing: A Validation Study—Paul B Blanch BA RRT and Michael J Banner PhD [Respir Care 1994;39(9):897-905]

1994 Allen & Hanburys Award

Best Original Paper Accepted for Publication from November 1993 through October 1994 ($2,000)

Respiratory System Behavior during Mechanical Inflation with Constant Inspiratory Pressure and Flow—Robert L Chatburn RRT, Mohamad F El-Khatib MS, and Paul G Smith DO [Respir Care 1994;39(10):979-988]

2 Papers Based on any OPEN FORUM Presentation ($1,000)

(1) Prediction and Assessment of Bronchodilator Response in Mechanically Ventilated Patients—Patricia J Wollam RRT, Carol L Kasper RRT, Michael J Bishop MD, and David J Pierson MD [Respir Care 1994;39(7):730-735]

(2) Flow-Triggering Does Not Decrease the Work of Breathing and Pressure-Time Product in COPD Patients—Kelly Jager RRT, Martin Tweeddale MB PhD, and Tammy Holland RRT [Respir Care 1994;39(9):892-896]

Best Papers Submitted by 1994 OPEN FORUM Participants Who Have Never Published As First Author ($500)

(1) Pulmonary Response to an Inhaled Bronchodilator in Infants with Suspected Airway Reactivity—William J Holt RRT RPFT

(2) Benefits Associated with a Respiratory Care Assessment-Treatment Program: Results of a Pilot Study—Kevin L Shrake MA RRT, John E Scaggs BS RRT, Kevin R England BA, Joseph Q Henkle MD, and Lanie E Eagleton MD

Radiometer Awards for Best Features

PFT Corner #52—Cardiopulmonary Exercise Testing in the Preoperative Evaluation of Patients with Lung Cancer by DeeAnn Miller RRT and Jeff Wilson MD [Respir Care 1994;39(7):757-761] *($333)*

Test Your Radiologic Skill—Hemoptysis and Dyspnea in a Young Woman by Paul Lange MD, Kevin McCarthy RCPT, James K Stoller MD, and Daniel Laskowski RPFT [Respir Care 1994;39(3):242-249] *($333)*

Test Your Radiologic Skill—Radiographic Findings in a Blunt Trauma Patient by Grace Nadell BS and Frederick W Clevenger MD [Respir Care 1993;38(12):1423-1427] *($333)*

1995 Call for Abstracts

RESPIRATORY CARE • OPEN FORUM

The American Association for Respiratory Care and its science journal, RESPIRATORY CARE, invite submission of brief abstracts related to any aspect of cardiorespiratory care. The abstracts will be reviewed, and selected authors will be invited to present papers at the OPEN FORUM during the AARC Annual Meeting in Orlando, Florida, December 2-5, 1995. Accepted abstracts will be published in the November 1995 issue of RESPIRATORY CARE. Membership in the AARC is not necessary for participation.

SPECIFICATIONS—READ CAREFULLY!

An abstract may report (1) **an original study,** (2) **the evaluation of a method or device,** or (3) **a case or case series.** Topics may be aspects of adult acute care, continuing care/rehabilitation, perinatology/pediatrics, cardiopulmonary technology, health-care delivery. The abstract may have been presented previously at a local or regional—but not national—meeting and should not have been published previously in a national journal. The abstract will be the only evidence by which the reviewers can decide whether the author should be invited to present a paper at the OPEN FORUM. Therefore, *the abstract must provide all important data, findings, and conclusions.* Give specific information. Do not write such general statements as "Results will be presented" or "Significance will be discussed."

Essential Content Elements

An original study abstract *must* include (1) Introduction: statement of research problem, question, or hypothesis; (2) Method: description of research design and conduct in sufficient detail to permit judgment of validity; (3) Results: statement of research findings with quantitative data and statistical analysis; (4) Conclusions: interpretation of the meaning of the results. **A method/device evaluation** abstract *must* include (1) Introduction: identification of the method or device and its intended function; (2) Method: description of the evaluation in sufficient detail to permit judgment of its objectivity and validity; (3) Results: findings of the evaluation; (4) Experience: summary of the author's practical experience or a lack of experience; (5) Conclusions: interpretation of the evaluation and experience. Cost comparisons should be included where possible and appropriate. **A case report** abstract *must* report a case that is uncommon or of exceptional teaching/learning value and must include (1) patient data and case summary and (2) significance of case. Content should reflect results of literature review. The author(s) should have been actively involved in the case and a case-managing physician must be a co-author or must approve the report.

Abstract Format and Typing Instructions

Accepted abstracts will be photographed. First line of abstract should be the title in all capital letters. Title should explain content. Follow title with names of all authors (including credentials), institutions(s), and location. Underline presenter's name. Type or electronically print the abstract *single spaced in the space provided on the abstract blank.* Insert only one letter space between sentences. Text submission on diskette is encouraged but must be accompanied by a hard copy. Identifiers will be masked (blinded) for review. Make the abstract all one paragraph. Data may be submitted in table form *and simple figures may be included provided they fit within the space allotted.* No figures, illustrations, or tables are to be attached to the abstract form. Provide all author information requested at the bottom of abstract form. A clear photocopy of the abstract may be used. Standard abbreviations may be employed without explanation. A new or infrequently used abbreviation should be preceded by the spelled-out term the first time it is used. Any recurring phrase or expression my be abbreviated if it is first explained. Check the abstract for (1) errors in spelling, grammar, facts, and figures; (2) clarity of language; and (3) conformance to these specifications. An abstract not prepared as requested may not be reviewed. Questions about abstract preparation may be telephoned to the editorial staff of RESPIRATORY CARE at (214) 243-2272.

Deadline Allowing Revision

Authors may choose to submit abstracts early. Abstracts received by March 15 will be reviewed and the authors notified by April 22. Rejected abstracts will be accompanied by a written critique that should in many cases enable authors to revise their abstracts and resubmit them by the final deadline (May 27).

Final Deadline

The mandatory Final Deadline is May 27 (postmark). Authors will be notified of acceptance or rejection *by letter only*—to be mailed by August 15.

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Calendar of Events

AARC & AFFILIATES

December 9 in Las Vegas, Nevada. The AARC and its Board of Medical Advisors present a postgraduate course for medical directors and other physicians the day before the Annual Meeting. The program is approved for 6 Category 1 credit hours of the Physician's Recognition Award of the American Medical Association. Lecture topics include ethical dilemmas in the ICU, TB as an occupational hazard, cost-effective management of critical illness, and all aspects of providing respiratory care by protocol. Contact the AARC at (214) 243-2272 or fax (214) 484-2720 to request that a complete course description and registration form be sent to your medical director or other interested physician.

December 10-13 in Las Vegas, Nevada. The AARC presents its 40th Annual Convention and Exhibition, "A New Vision," at the Las Vegas Convention Center. For information, contact the AARC at (214) 243-2272, fax (214) 484-2720.

February 14-17, 1995 in Reno, Nevada. The NSRC and the American Lung Association of Nevada present the 14th Annual High Sierra Critical Care Conference at the Peppermill Hotel/Casino. The 4-day conference covers critical care topics in adult, pediatric, and neonatal medicine. Contact Colleen Banghart, American Lung Association of Nevada, PO Box 7056, Reno NV 89510.

February 16–17, 1995 in Atlanta, Georgia. The Perinatal/Pediatric Committee of the GSRC announces a perinatal/pediatric review course at Piedmont Hospital. Contact David Ellwanger, Respiratory Care Services, Piedmont Hospital, 1968 Peachtree Rd., Atlanta, GA 30309, (404) 605-3657.

March 12-15, 1995 in Denver, Colorado. The AARC and the National Jewish Center for Immunology and Respiratory Medicine announce the call for abstracts for the 5th International Conference on Pulmonary Rehabil-itation and Home Ventilation at the Hyatt Regency Hotel. The abstract deadline for poster/oral presentations on original research/clinical observations is Nov 30, 1994. Pre- and post-conference postgraduate workshop topics include pulmonary rehabilitation, home ventilator care, respiratory sleep disorders, nicotine dependency treatment, and transtracheal oxygen. The program is endorsed by the American College of Chest Physicians; program chairman is Barry Make MD. Contact the National Jewish Office of Professional Education at (303) 398-1000.

OTHER MEETINGS

February 5-8, 1995 in Breckenridge, Colorado. The American College of Chest Physicians sponsors "Cardiopulmonary Wellness and Rehabilitation" at The Village at Breckenridge Resort. Contact Arlene Karavich, American College of Chest Physicians, 3300 Dundee Rd, Northbrook IL 60062-2348. (708) 498-1400.

February 27–March 3, 1995 in Keystone, Colorado. The Extracorporeal Life Support Organization announces the 11th Annual Children's National Medical Center ECMO Symposium. Featured topics include lung transplants for the ECMO population, postoperative ECLS for the cardiac patient, clinical and research issues of liquid ventilation, and nitric oxide. Contact Cynthia Poindexter at (202) 884-5018.

April 1-7, 1995 in Miami, Florida. The Ventilation Assisted Children's Center (VACC) of the Division of Pediatric Pulmonology in Miami Children's Hospital hosts its annual VACC Camp for ventilation assisted children and their families. The program includes swimming, field trips, structured games, and campsite entertainment. The campsite, the Leisure Access Center at metro Dade county's AD Barnes Park, is a handicapped-accessible urban park located 2 miles from the hospital. Medical staff and equipment are available 24 hours-a-day. Contact Cathy Klein, VACC Program Coordinator, Division of Pediatric Pulmonology, Miami Children's Hospital, Suite 203, 3200 SW 60 Court, Miami FL 33155-4076. (305) 662-VACC.

May 5–7, 1995 in Atlanta, Georgia. The Egleston Children's Hospital ECMO Program sponsors the 5th Annual Southeastern ECMO Conference at the Westin Peachtree Plaza. The conference is designed specifically for the ECMO technical specialist. Contact Michelle Heard, RN, at (404) 315-2593.

AARC
American Association for Respiratory Care
40th Annual Convention and Exhibition
December 10-13, 1994 • Las Vegas, Nevada

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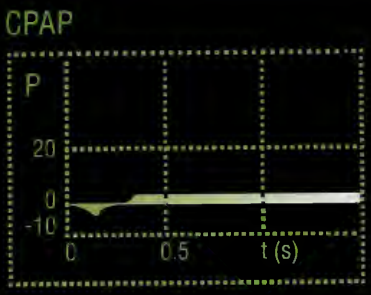

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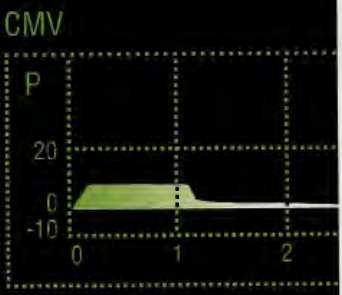

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